Exhibit 29

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

IN RE: ACETAMINOPHEN - ASD-ADHD PRODUCTS LIABILITY LITIGATION	)	MDL No. 3043
	)	Case No. 1:22-md-03043-DLC
THIS DOCUMENT RELATES TO: All Cases	)	JUDGE DENISE COTE

CONFIDENTIAL - PURSUANT TO PROTECTIVE ORDER

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Friday, September 8, 2023

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Video-Recorded Oral Deposition of MITCHELL R. McGILL PhD held at the offices of Quattlebaum Grooms & Tull PLLC, 111 Center Street, Suite 1900, Little Rock, Arkansas, commencing at 8:46 a.m. CDT on the above date, before Michael E. Miller, Fellow of the Academy of Professional Reporters, Certified Court Reporter, Registered Diplomate Reporter, Certified Realtime Reporter and Notary Public.

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MITCHELL R. McGILL PhD

September 8, 2023

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P R O C E E D I N G S

September 8, 2023, 8:46 a.m. CDT

THE VIDEOGRAPHER: We are now on the record. My name is Dan Lawlor. I'm the videographer representing Golkow Litigation Services.

Today's date is September 8th, 2023, and the time is 8:46 a.m.

This video deposition is being held in Little Rock, Arkansas in the matter of Acetaminophen Tylenol ASD-ADHD Products Liability Litigation, MDL No. 3043.

The deponent is Mitchell McGill.

Counsel will be noted on the stenographic record.

The court reporter is Mike Miller and will now swear in the witness.

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MITCHELL R. McGILL PhD, having been duly sworn, testified as follows:

EXAMINATION

BY MR. JANUSH:

Q. Good morning, Dr. McGill.

A. Good morning.

Q. Dr. McGill, in 2013, you received your doctorate in toxicology from the University of Kansas Medical Center; is that right?

A. That's correct.

Q. And you are not a neurologist; is that correct?

A. I'm not.

Q. And you are not an epidemiologist, true?

A. I am not an epidemiologist.

Q. And you're not a medical doctor, right?

A. I am a PhD.

Q. But you're not a medical

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doctor, right?

A. Correct.

Q. Okay. And aside from a review article you wrote with your wife, have you ever actually studied autism, the disease state?

MR. COHEN: Objection to the form.

A. Aside from that article, I have not done original research on the subject of autism.

BY MR. JANUSH:

Q. Okay. And that article wasn't original research either, right? It was a review of articles, right?

A. It's a narrative review of the literature. When we write a review like that, we try to review as much of the relevant literature as we possibly can and evaluate it critically so there is original analysis.

Q. But it's original analysis of other people's publications, right?

A. It's original analysis of prior studies that have been performed by others.

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Q. Okay. And have you ever studied ADHD before?
A. Aside from what we mentioned about it in that review article, I have not done original research on ADHD.
Q. Do you have any experience publishing in the field of developmental neurotoxicity or DNT?
A. I don't believe I've published any original research articles in that area.
Q. Do you have experience -- well, you're not a teratologist either, right?
A. My expertise is not in teratology. Teratology could be considered a component of toxicology, and I am a toxicologist.
Q. But you're not a teratologist, right?
MR. COHEN: Objection, asked and answered.
A. Well, again, teratology is -- could be considered sort of a subfield of toxicology, so I'm trained as a toxicologist. I don't do -- I don't do original research on the -- what would widely be considered

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teratology.
BY MR. JANUSH:
Q. In any bios that you have online, within your university, LinkedIn or otherwise, do you hold yourself out to others as a teratologist?
A. I don't believe so, no.
Q. Are you an expert on the fetal brain?
A. I'm an expert on the subject of acetaminophen metabolism, and the questions at hand here are about acetaminophen metabolism in the brain, particularly the fetal brain, after maternal ingestion of therapeutic doses of acetaminophen. So in that sense, I'm an expert on this subject matter.
MR. JANUSH: Move to strike as nonresponsive.
BY MR. JANUSH:
Q. Do you remember my question?
MR. COHEN: Object to the form.
MR. JANUSH: I asked a simple question.
BY MR. JANUSH:

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Q. Are you an expert on the fetal brain? I'm not asking about acetaminophen. Are you an expert on the fetal brain?
MR. COHEN: Object to the form.
A. The "fetal brain" is a rather broad topic. Again, I'm an expert on acetaminophen metabolism, and I think that's relevant to the question at hand here of whether or not acetaminophen can be converted to NAPQI within the fetal brain.
BY MR. JANUSH:
Q. I appreciate that you'd like to determine what's relevant, but for the moment, I'm going to be asking the questions and you're going to be answering them or it's going to be a very long day.
So I'm just asking: Are you an expert on the fetal brain? I'm not talking about acetaminophen. We're not talking about your assignment or reason you're here today.
Are you an expert on the fetal brain?
MR. COHEN: Object to the form. I don't think it's appropriate to lecture the witness on his role.

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MR. JANUSH: Well, I've asked it twice already. I'm not getting an answer to the very straightforward question. It has one, two, three, four, five, six, seven, eight words. Eight words.
BY MR. JANUSH:
Q. Are you an expert on the fetal brain? That's all I'm asking.
MR. COHEN: Object to the form.
A. The words are fairly broad, as I stated. Again, I'm an expert in acetaminophen metabolism, and the question at hand here is whether or not the fetal brain is metabolized to form -- excuse me, can metabolize acetaminophen to form NAPQI, and as an expert in acetaminophen metabolism, I'm qualified to comment on that.
BY MR. JANUSH:
Q. I didn't ask you that. Do you understand that?
MR. COHEN: Object to the form.
BY MR. JANUSH:
Q. I'm not asking you what you're qualified to comment on with respect to

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today's assignment or the reason you're here today. I'm only asking if you're an expert on the fetal brain.

MR. COHEN: Object to the form.

BY MR. JANUSH:

Q. Let me ask it differently: What have you published on the fetal brain?

A. Aside from what we've discussed in that review that again involved critical analysis and evaluation of the literature that is relevant to that, I've not published original research articles dealing with the fetal brain.

Q. So as someone who has never published original research articles dealing with the fetal brain, do you hold yourself out as an expert on the fetal brain?

A. Again, I don't feel that that can be answered with a yes or a no. I've given my answer, and I'll probably just repeat it again, which is that I'm an expert in acetaminophen metabolism, and I can speak to that in the fetal brain.

Q. You understand that this transcript is going to be appended to

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briefing before a federal judge who's going to have the opportunity to read my questions and your answers, right?

A. Yes.

Q. Fair to say you want to be really responsive and accurate in response to my questions?

MR. COHEN: Object to the form. You don't need to lecture the witness on his role --

MR. JANUSH: You can only say object to the form, Counsel. That's warning number one. Object to the form --

MR. COHEN: No.

MR. JANUSH: That is the deposition protocol that I helped enter in this case on behalf of the plaintiffs, and I negotiated with the defendants' counsel, one of which was not you, and that is the order. "Object to form" are the only words you may use, period.

MR. COHEN: With all due respect, Mr. Janush, I acknowledge the

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court's order and that limitation, but when an attorney, an opposing attorney, is --

MR. JANUSH: You don't have to give a speech.

MR. COHEN: Excuse me, let me finish. Is lecturing a witness on how a witness needs to answer his questions, that's outside the scope of that limitation.

BY MR. JANUSH:

Q. I didn't lecture. I asked if you understood that the judge is going to be reading this transcript.

MR. COHEN: And that's a lecture. Just ask your questions.

MR. JANUSH: And just say objection to form.

MR. COHEN: Unless there's inappropriate conduct being conducted.

MR. JANUSH: Just say objection to form or we will --

MR. COHEN: Continue, Counsel.

MR. JANUSH: Or we will mark this and file a motion literally by

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Monday.

MR. COHEN: You may continue.

MR. JANUSH: Oh, I don't need your permission to continue, but I appreciate your courtesy.

BY MR. JANUSH:

Q. Are you a pharmacologist?

A. My PhD is in toxicology, and the program in which I was trained, that required initial training in pharmacology and then additional classes in toxicology.

Q. Are you a pharmacologist? I'm not talking about your training. Are you a pharmacologist?

A. Again, I'm trained in pharmacology as part of my PhD training, part of my PhD coursework, so I have pharmacology training and I have additional training in toxicology.

Q. Aside from your training, are you offering yourself in this case as an expert in pharmacology?

A. I'm offering my help in this case as an expert in specifically acetaminophen metabolism and toxicity.

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Q. So is that a no?
A. I wouldn't call it a no. It's -- insofar as it is relevant to acetaminophen metabolism and toxicity, I can comment on the pharmacology.
Q. I'm not asking what you can comment on. I asked if you're offering yourself as an expert in pharmacology.
MR. COHEN: Object to the form.
A. Again, I'm offering myself as an expert -- maybe I can restructure my response a little bit, if that would be helpful.
I'm offering my services or my help or expert -- expertise in this case as an expert in acetaminophen metabolism and toxicity, and pharmacology insofar as it is relevant to those questions.
BY MR. JANUSH:
Q. Would you agree that in your report you devote a fair amount of your report to pharmakinetics [sic]?
A. Pharmacokinetics.
Q. Sorry, yes, pharmacokinetics.
A. Yes. Well, I specifically

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address the pharmacokinetics of acetaminophen.
Q. You offer criticisms of the opinions proffered by Dr. Louie, who actually is a pharmacologist; is that right?
MR. COHEN: Objection to form.
A. I'm -- criticisms with respect to what? With respect to pharmacokinetics?
BY MR. JANUSH:
Q. I'm just addressing that in your report you criticized Dr. Louie, who actually is a pharmacologist, true?
MR. COHEN: Object to the form.
A. I'm not criticizing Dr. Louie himself. I'm criticizing some of the claims that he's made, critically evaluating some of the claims that he's made.
BY MR. JANUSH:
Q. Historically, Dr. McGill, throughout your academic career and after receiving your doctorate in 2009, is it fair to say that you've primarily been looking into liver damage arising from acetaminophen use?
A. I just want to make sure I

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heard the first part. Can you restate it?
Q. Sure can.
Historically, throughout your academic career and after receiving your doctorate in 2009, is it fair to say you have primarily been looking into the issue of liver damage arising from acetaminophen use?
A. Most of my studies have focused on -- on the -- on acetaminophen hepatotoxicity. However, we've also done research on acetaminophen metabolism and toxicity in the cochlea, which is part of the auditory nervous system, as well as in the lung.
Q. Right. And the cochlea was one study, correct?
A. Actually --
Q. One published piece of literature.
A. Actually, three published pieces of literature. So one was looking at -- it was published -- I forget the year, I'm sorry, at the moment. But it was on the subject of -- what we did in that study was we gave mice acetaminophen and we looked at

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whether or not it causes, number one, hearing loss; number two, whether or not there's acetaminophen-protein adducts or glutathione depletion as surrogate markers of NAPQI formation.
Another original study was on whether or not P450s are expressed in the cochlea, especially compared to the liver, and although we -- and we -- and the discussion of that, we addressed the implications for acetaminophen.
And then the third was the review that we've discussed.
Q. Sure.
How many total publications concerning acetaminophen have you published approximately?
A. I don't recall the exact number, but approximately -- I think it's around 75.
Q. And so you just ticked off like four studies out of 75 that didn't have to do with acetaminophen use specifically associated with liver damage, right?
MR. COHEN: Object to the form.

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BY MR. JANUSH:
Q. In other words, out of approximately 75 studies, four of your studies didn't have to do with liver damage, right?
A. It's hard for me to say without seeing the list --
Q. Approximately. Try to move this along so we don't have to spend a lot of time on prefatory background.
MR. COHEN: Object to the -- object to the statement.
Go ahead.
A. My concern about the way you're phrasing the question is that counting number of publications is a valid way to assess somebody's expertise in an area.
MR. JANUSH: Move to strike, nonresponsive. Not what I asked.
MR. COHEN: I'm sorry, he wasn't even finished. Please don't interrupt the witness.
A. I think, you know, there are other factors to consider.
///

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BY MR. JANUSH:
Q. Do you understand I'm only asking you, out of your total history of publishing scientific literature, what number of studies had nothing to do with liver damage?
MR. COHEN: Object to the form.
Go ahead.
A. I understand your question. I think we've discussed that.
BY MR. JANUSH:
Q. I just want an answer.
A. And my answer is I don't think that's an appropriate way to evaluate -- counting papers is an appropriate way to evaluate expertise.
Q. You don't get to -- you do not get to judge what is an appropriate way to evaluate anything today. I get to ask questions, and you have to answer my questions. And if you're not going to, I'm going to call Judge Cote and read this question and answer into the record and get a ruling within the next hour to cause you to actually listen to my question and answer my

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question.
MR. COHEN: Okay.
BY MR. JANUSH:
Q. Do you understand me?
MR. COHEN: I'm going to make an objection.
MR. JANUSH: You can, but this is -- I have made my record and I don't need to say more. I'm going to call the court if I can't get an answer.
The witness does not get to make judgments in response -- if he doesn't like the question. That is not how this works.
MR. COHEN: He --
MR. JANUSH: You know it. So if you need to take a break, walk the witness out in the hall and give him some proper tutelage about how to answer deposition questions, I'm going to encourage you to do that.
So I'm going to now, on the record, offer you that break before I take this further.

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MR. COHEN: He answered your question.
MR. JANUSH: I'm going to offer you that break. Are you saying you don't want to take a break?
MR. COHEN: I don't need to take a break.
MR. JANUSH: Okay.
BY MR. JANUSH:
Q. My question was: Out of 75 --
MR. COHEN: I'm just going to state for the record that I don't appreciate the lecturing to the witness.
MR. JANUSH: Out of --
MR. COHEN: Excuse me. Let me just finish at least; otherwise, we'll be talking over each other. He does not need to be lectured on how to be a witness.
MR. JANUSH: He sure does.
MR. COHEN: Your job is to ask questions.
MR. JANUSH: And his job is to answer them. What I asked, not what

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he wants to answer.
MR. COHEN: Maybe it's the question, Counsel.
MR. JANUSH: The question is --
MR. COHEN: You're a capable --
MR. JANUSH: No more. No more.
MR. COHEN: No, no.
MR. JANUSH: David, no more.
MR. COHEN: You're a capable lawyer.
MR. JANUSH: No more, David.
MR. COHEN: Rephrase your question.
MR. JANUSH: No more.
BY MR. JANUSH:
Q. You've published approximately 75 pieces of scientific literature, true? Yes or no?
A. No, I've published approximately a hundred.
Q. A hundred --
A. I apologize, I need to rephrase that. I published approximately 100 peer-reviewed published papers.
Q. Okay.

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A. In addition to that, approximately a dozen textbook chapters.
Q. And of the approximate 100 peer-reviewed published papers, how many of the approximate 100 had to do with liver and acetaminophen?
A. I wasn't quite finished with my answer.
So 100 peer-reviewed manuscripts approximately. Approximately 12 book chapters that I can recall off the top of my head, and somewhere in the range of 50 to 60 published abstracts.
Q. Now will you answer my question?
A. Can you restate the question, please.
Q. Of -- out of the total number of publications you've published, how many didn't have to do with the liver?
A. Including abstracts and book chapters, I cannot recall the exact number. It's more than four.
Q. Okay. Is this the first time in your career testifying as an expert?

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A. Yes.
Q. Is this the first time you are testifying in a deposition?
A. Yes.
Q. In this case, what entity is your agreement with?
A. I don't recall having a written agreement. I think my -- I think my agreement is with Butler Snow.
Q. Okay. Do you understand which corporate defendants you're working on behalf of?
A. I'm aware of at least one of them.
Q. And who is that?
A. The one that I'm aware of is J&J.
Q. Okay. The maker and seller of Tylenol, right?
A. In the United States.
Q. How did you come to serve as an expert in this case?
A. I was sought by someone from Butler Snow.
Q. Do you currently teach at the

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University of Alabama?
A. No.
Q. I mean of Arkansas. Sorry. I meant to say Arkansas.
MR. WATTS: He's going to the game.
MR. JANUSH: I'm going to Alabama literally tonight, so forgive me.
(Comments off the stenographic record.)
THE WITNESS: You want to --
BY MR. JANUSH:
Q. Do you currently teach at the University of Arkansas?
A. I teach at the University of Arkansas for Medical Sciences.
Q. Okay.
A. Which is part of the University of Arkansas system.
Q. What do you teach?
A. I teach -- so I teach PhD students -- first of all -- well, there's two different types of teaching, right. There's formal classroom teaching and then there's

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mentorship, which is also a type of formal instruction. It's just practical hands on in the laboratory guiding through research. So I teach graduate students, PhD students in the lab through that mentorship type of teaching.

I also lecture on drug metabolism and hepatotoxicity to graduate students. I also teach a course to public health students on -- currently teach a course to public health students on FDA regulations, and I also teach pathology residents, so primarily physicians in a pathology residency program, teach them clinical toxicology as well as a number of other subjects.

Q. Are you a teacher that teaches like Monday to Friday?

A. Monday through Friday? That kind of depends. That's a little bit hard to answer because some classes are online and asynchronous so they go technically throughout the day every week.

In terms of physical, in-person lectures -- I'm sorry, I didn't know if I needed to pause.

Q. I'm listening.

A. In terms of in-person lectures, I teach -- so I teach the drug metabolism toxicity to PhD students in the spring, and then I teach pathology residents all throughout the year, but it's not necessarily every week. It's usually two to three days a week, and it may be one to two weeks a month typically.

Q. Did you have an opportunity to review the CV, your résumé and appendices to your CV that was attached to your expert report?

A. Yes.

Q. Is it complete?

A. Yes.

Q. Any changes you need to make before we begin this deposition?

A. Let me rephrase my prior answer. It's complete as of the date that's listed at the top of my CV.

Q. Okay. What have you done since the date you submitted your expert report that would modify your CV?

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A. Off the top of my head, I'm not -- could you produce the document so I can take a look at it, just in case there's --

Q. I'm just asking if something -- I don't want to spend a lot of time on this. I'm just asking if something comes to your mind that you've done that isn't addressed in your CV.

A. Well, I'm trying to be cautious, you understand. As you mentioned, the judge will see this. I'm under oath. So I'd prefer to see a document.

Q. That's okay. We'll move on. If it was accurate as of the date that you submitted your report, that's good enough for me.

How did you prepare for today's deposition?

A. So I wrote my report. In the process of writing my report, I reviewed a substantial amount of -- I reviewed the literature that you've seen, the materials for the case. So that was an enormous part of my preparation.

Of course, my regular work and my career is -- some of it, at least, has relevance to the case, so I suppose you could consider that part of my preparation as well.

I -- again, this is -- since this is the first time I'm doing a deposition, I have asked questions about how to conduct myself and things of that nature.

Q. Who did you meet with to prepare for your deposition?

A. Well, again, since part -- the greater part of my preparation for this deposition was in preparing my report and reviewing the literature, so the majority of that time was just me --

Q. Did you meet with attorneys?

A. I have met with counsel.

Q. Who did you meet with?

A. I met with Mr. Cohen, Ms. Lucas. I don't recall exactly. You know, some people I just met in passing.

Q. On how many occasions did you meet with Mr. Cohen and Ms. Lucas?

A. I don't recall the number.

Q. More than ten?

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A. I don't know. I don't recall the number.
Q. Can't give an answer at all, like even if you were to estimate?
A. Again, being under oath and as you mentioned, the judge is watching -- will watch this, I don't feel comfortable answering without being certain.
(Whereupon, Deposition Exhibit P801, McGill Expert Report, was marked for identification.)
(Whereupon, Deposition Exhibit P801B, McGill First Supplemental Materials Reference List, was marked for identification.)
BY MR. JANUSH:
Q. Dr. McGill, I'm going to hand you what I'm marking as -- I've marked as Plaintiffs' Exhibit 801 and 801B. 801 is your report. 801B -- 801B is the addendum we received yesterday, the supplemental materials reference list.
Do you recognize 801 and 801B?
A. Yes.
Q. Dr. McGill, where in your

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report do you identify and describe the methodology that you employed to reach the opinions you offer concerning pharmacokinetics and acetaminophen?
A. I didn't describe the methodology in detail within the report. I think it's evident from the structure of the report. I'd be happy to share my methodology with you, if you'd like.
Q. Yeah, I'd like you to describe your methodology.
A. Sure.
So I applied the same standard that I apply in my everyday academic career and my scientific work, and that is following the scientific method.
So the scientific method, as you may be aware, progresses through a number of steps. There's observation. So you observe a phenomenon, an effect of some kind. Based on that observation, you formulate a hypothesis.
Once you have a hypothesis, you make predictions based on your hypothesis, and then you test those predictions

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experimentally.
Once you've tested them, if necessary, you return to your hypothesis and make revisions, and then new predictions and new testing. Once you get to a point where further testing is no longer necessary, you would publish that data, the information that you have, and then hopefully others will replicate it.
And so in a case like this, I think the observation or the suggestion has been made, and so based on that, there's a hypothesis that I've been asked to address, which -- which is described in my report; does acetaminophen -- is acetaminophen converted to NAPQI or is there NAPQI present at all in the brain after maternal ingestion of therapeutic doses of acetaminophen -- excuse me -- is there NAPQI in the fetal brain after maternal ingestion of therapeutic doses of acetaminophen.
So the prediction -- if that's our hypothesis and our -- what's called your -- so you would state your hypothesis as a falsifiable statement. So your hypothesis

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might be that acetaminophen is converted to NAPQI in the brain.
So then the prediction that you would make -- and let me clarify. The null hypothesis, which is also an important hypothesis, is that that doesn't happen.
So the prediction that you would make based on the hypothesis is, for example, one prediction you could make, that I personally made, is that if there is NAPQI present in the brain after acetaminophen exposure, then you would see acetaminophen-protein adducts in the brain.
And so I'm not doing the work myself here, right, so as opposed to myself testing that prediction, I look in the literature to see if anyone else has tested it. In this case it has been tested and it's found that there's no NAPQI present in the brain, even after massive overdoses of acetaminophen, but we can, of course, get into that later.
And so I see those -- that's an example of how I would approach it. And then also look for people who have replicated

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those data.
Q. You started out your answer long ago by saying that part of the scientific method includes testing and further testing, did you not?
MR. COHEN: Object to the form.
A. The method -- again, the progression is observation, hypothesis, prediction, testing, revision, if necessary, and then replication.
BY MR. JANUSH:
Q. What testing did you perform as part of your scientific method?
A. Yeah, as I stated in my answer, I didn't do the testing myself in this case because I'm -- I was asked to review the literature, right? And so instead of doing it myself, I look in the literature to see if anyone else has made the same predictions or tested the same predictions.
Q. Fair to say that tests concerning developmental neurotoxicology are particularly relevant in this case?
A. Well, the questions that I've been asked to address are about does

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acetaminophen, number one, is it converted to NAPQI in the brain or is there NAPQI present in the brain, particularly in the fetus after maternal ingestion of therapeutic doses, and then also is there oxidative stress in the brain and is -- is, basically, AM404 a plausible metabolite that could mediate biological effects after therapeutic doses of acetaminophen.
Q. Where is your hypothesis listed in your report?
A. Well, again, I think it's evident from the structure of the report, so --
Q. It's not evident to me, so can you point me to the page and paragraph where it's listed?
MR. COHEN: Object to the form.
I don't think he was finished.
A. So particularly if you look at paragraph 4. I'll just wait a moment.
(Pause.)
BY MR. JANUSH:
Q. Is that the paragraph that begins with the reports of plaintiffs'

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experts that you reviewed?
A. Correct.
Q. And --
A. So in that paragraph, I state that those reports include speculation on various mechanisms by which maternal use of acetaminophen might result in ASD or ADHD in offspring.
The plaintiffs' experts proposed mechanisms of acetaminophen injury to the embryonic/fetal brain -- for the record, I'm quoting from my report -- that include a formation of N-acetyl-p-benzoquinone imine, or NAPQI, however you prefer to say it, the potentially hepatotoxic metabolite in the brain -- the hepatotoxic metabolite, the potential presence of that in the brain, I should say, oxidative stress in the brain and the production of AM404.
I go on to state that -- state my conclusions, which is there's no scientific evidence of NAPQI formation in the human embryonic or fetal brain sufficient to cause injury following maternal ingestion of

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therapeutic doses of acetaminophen.
There's no scientific evidence of oxidative stress in the human embryonic or fetal brain following maternal ingestion of therapeutic doses of acetaminophen.
And there's no scientific evidence that AM404 exists in the human embryonic or fetal brain or has adverse biological effects following maternal ingestion of therapeutic doses of acetaminophen.
So I've laid out what mechanisms the plaintiffs propose that I was asked to address. And that is the hypothesis. That -- those are the hypotheses.
Q. And what's your null hypothesis?
A. Right. So for each one, the null hypothesis would be that there isn't NAPQI in the brain; there isn't oxidative stress in the brain; and that you don't produce enough AM404 in the brain to have adverse effects on -- enough of those to have adverse effects in question, or at all in

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some cases.
Q. In order to arrive at opinions you're offering in your report, one of the things you did was review the report submitted by plaintiffs' experts, right?
A. I reviewed their reports, yes.
Q. And then you reviewed certain studies, right?
A. Yes.
Q. Anything else?
A. So in my review of the studies, the way that I approach that typically is I do a literature search using relevant search terms, and then when I identify literature that appears to be relevant from those searches, I examine those papers.
If they cite literature in those papers that may also be relevant, I review that information, those papers, and then -- so I obtain additional literature in that way. So through literature searches, through other literature that's cited in the papers that I get from those searches.
I also have done my own obviously extensive research in the area of

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acetaminophen metabolism and toxicity, and then in addition to that, defense counsel has provided a little bit of literature.
Q. Could you describe the criteria you employed to set -- to select the appropriate studies for your analysis? I understand that you've addressed that you used search terms, but I want the criteria, and then thereafter, I'm going to follow up with asking you about your specific search terms.
MR. COHEN: Object to form.
Go ahead.
A. So I used the same approach that I use anytime I'm evaluating the literature in my regular scientific work, so applying the same standards.
That approach is typically search at least one database, such as, for example, Medline or PubMed. They're essentially the same thing. And then I would perform that search using Boolean search terms. So for -- just as an example, since you alluded to search terms, one example I could give would be acetaminophen and brain

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or acetaminophen -- or brain and CYP2E1 and fetal. Those are just examples.
Once I've done that search, my approach then is to go back to the earliest study, so sort the studies by date, go back to the very first one and then work my way forward in time. Because understanding where we start helps me to understand where we are now, to how we get there.
As I go through those studies, I use what's a typical approach and what we could call a systematic review, which is a very common type of review that's often published, and where I initially review the title and abstract for relevance.
You know, so an example that I could give for nonrelevance might be there's a paper where they looked at, you know, the effect of a natural product on acetaminophen toxicity in the liver and then the effect of a natural product on something else in the brain. So the search terms that I use could yield something like that.
Well, that's not addressing the topic here, right? That's about some natural

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product in the brain and then also in the liver, so I would filter that out. I would consider that irrelevant.
So I would go through each paper step by step like that. Once I've collected all the papers that are relevant to the topic, then I go through and review them.
BY MR. JANUSH:
Q. We don't have your search terms, right? You didn't provide that to us in your report; is that right?
A. That's correct.
Q. So we can't reproduce your analysis, can we?
MR. COHEN: Object to the form.
A. Again, the approach that I used is very standard. Anyone has -- you know, PubMed is a publicly accessible database. Anyone can go in there and perform very similar searches, and it's a very -- in my field it's a very, very standard approach to a systematic review of the literature. So it's what I would expect most people to do.
BY MR. JANUSH:
Q. But while PubMed is widely

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available and I can go online and access it right now, would you agree that I don't have your search terms publicly available to reproduce your methodology as to how you selected your literature?

MR. COHEN: Object to form.

A. Well, I just provided a couple of examples of search terms. I did not list them in this report.

BY MR. JANUSH:

Q. Right. You would agree with me -- would you agree with me that the couple of examples you provided are -- are nowhere near the total search terms that you would have used, or are they?

Do they represent the search terms that you utilized and nothing more in arriving at your -- the literature you reviewed?

A. Well, so again, just to be clear, the literature that I reviewed comes not just from searches. It comes from studies referenced as -- referenced by the studies that came up in my -- the relevant studies that come up in my search terms. It

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comes from my own research, and it comes from some documents provided by the defense counsel.

Now, in terms of answering your question more directly, I don't recall the number of search terms that I used. And again, I -- as I've said, I didn't provide them directly in my report.

Q. What did you do to satisfy yourself that your search was exhaustive?

A. So again, that systematic approach is a common practice in the field. It's kind of the standard approach in my field to a review of the literature. It's done that way because it's an exhaustive approach.

Again, we're going back to the very beginning and moving forward. And again, I'm not just relying on the results that I get from that search. I look at references that are provided in those papers, so you get kind of a network of literature.

And one way you can tell you've pretty much seen what's out there is when you start seeing the same references over and

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over in your searches and in your review of the literature and that sort of thing.

But again, it's a -- that's a common approach and it's common because it's exhaustive.

Q. Are you aware that Dr. Powell and Johnson & Johnson Consumer Inc. used different search terms in their review of the preclinical literature?

MR. COHEN: Object to form.

A. Well, Dr. Powell and I are addressing different issues. Oh, I'm sorry, you mean between Johnson & Johnson and Dr. Powell there are differences?

I -- I have no information about Johnson & Johnson's searches.

BY MR. JANUSH:

Q. Do you know -- let me ask -- sorry, apologize, I'm going to ask a different question.

Are you aware of what search terms Dr. Powell used in his review of preclinical literature?

A. I reviewed Dr. Powell's report, but I don't remember exactly what he said

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about his methodology.

Q. So two different scientists with two different search methodologies and two different sets of search terms might come up with different results, right?

MR. COHEN: Object to form.

A. Well, that's why you employ multiple different search terms to avoid -- so my expectation would be if I did only one search and the other individual did only one search with different search terms, there would be -- assuming it's on the same topic, right -- then there would be considerable overlap, but there might be a few different studies. But that's why you use multiple search terms.

So if I used multiple search terms and the other person uses multiple search terms, then I would expect us to arrive at nearly identical results.

BY MR. JANUSH:

Q. Is transparency important in science?

A. That's, again, quite a broad question. Transparency in terms of what

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you've done and the data you've collected?
Q. Yes.
A. Yes.
Q. What does transparency mean to you in fulfilling your role as an expert in this case?
MR. COHEN: Object to the form.
A. Well, I mean, I've -- in terms -- if we're still just talking about, right, the scientific content, being transparent is sharing the results of my review of the literature and doing so accurately.
BY MR. JANUSH:
Q. If I asked you right now, could you provide me, after this deposition ended, with a list of your search terms and the way you approached your searches to obtain the literature you utilized in your report, could you do it?
MR. COHEN: Object to the form.
A. I could provide you with -- excuse me -- multiple search terms that I believe would yield the same studies.
///

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BY MR. JANUSH:
Q. How about the actual search terms that you utilized, could you provide me with that?
MR. COHEN: Object to the form.
A. I...
BY MR. JANUSH:
Q. In other words, did you retain your search terms?
A. I'm trying to consider the question and answer it accurately.
Again, I could easily provide you a list of search terms that would yield the same results.
Q. You could provide me with a list of search terms that would yield the same results as all of the literature that you have addressed in your report; is that your testimony today?
MR. COHEN: Object to the form.
A. At least the majority of the results, yeah.
BY MR. JANUSH:
Q. Would you agree to do that after this deposition ends?

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MR. COHEN: Object to the form. We'll take it under advisement.
A. I -- I don't think I can agree -- I would agree to anything without discussing it -- without thinking it over and discussing it.
BY MR. JANUSH:
Q. Is it good or bad for a scientist to cherry-pick literature?
MR. COHEN: Object to the form.
A. Well, personally, I try to avoid it. I think at least one of your expert witnesses has done that, and --
MR. JANUSH: Move to strike, nonresponsive.
BY MR. JANUSH:
Q. I just asked you if it's a good thing or a bad thing to cherry-pick literature when serving as an expert.
MR. COHEN: Object to the form.
A. Sorry, when serving as an expert specifically? Yeah, I -- I would not cherry-pick literature. Again, I think at least one of your plaintiff experts has done so.

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MR. JANUSH: Move to strike the latter part of the gratuitous answer beginning with "at least" and ending with "done so."
BY MR. JANUSH:
Q. Were there any limitations or challenges you encountered while applying your claimed scientific method to your assignment?
MR. COHEN: Object to the form.
A. Sorry, can you ask the question again?
BY MR. JANUSH:
Q. Were there any limitations or challenges that you encountered when applying your claimed scientific method to your assignment in this case?
MR. COHEN: Same objection.
A. No, not off the top of my head. Again, my approach is standard in the field.
BY MR. JANUSH:
Q. As part of your literature review, did you look at and consider the studies addressed before your expert report was due by plaintiffs' experts?

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A. Can you ask the question -- I want to make sure I understand --
Q. You understand that before your expert report was due, plaintiffs had to serve their expert reports, right?
A. Yes.
Q. And you -- you had an opportunity to receive those expert reports, right?
A. Yes.
Q. And you had an opportunity to review those reports, right?
A. Yes.
Q. And you did review them, right?
A. Yes, my report contains some responses to those.
Q. I understand that.
Did you -- how did you go about addressing which of the articles or pieces of literature you would include in your materials reviewed list?
A. Well, I mean, we included everything that I -- I referenced, every study that I went over in my report as well as other relevant studies that we -- that I

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found in the process of doing my literature searches and reviewing the report as well as any relevant literature that I identified when reviewing the plaintiffs' experts' reports.
I mean, essentially, with regard to the reference list, it just includes basically everything that we -- that I looked at.
Q. Your reference list includes everything you looked at in this case. Fair to say?
A. Except those things that I ruled out as irrelevant, as I described when discussing my methodology.
Q. What types of literature did you rule out as irrelevant?
A. Yeah, I described that in my previous response. So an example would be, you know, let's say again, search term is acetaminophen and brain, right? That's a Boolean search term, so return anything that mentions both acetaminophen and the brain.
So -- but there might be a study where, for example, they're interested

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in -- let's say they're testing a natural product, a dietary supplement, botanical extract, something like that. They want to know if it affects the liver, and then they may also have an additional question about, you know, does it have any impact on the brain.
So they do two different studies, but they are in the same paper, but the study relative to the brain has nothing to do with acetaminophen. So that would obviously not be a relevant paper and I would exclude that.
Q. Fair to say that "acetaminophen" was a fundamental term in your searches?
A. For parts of -- for some of my searches. There are others where I was just looking at P450 levels in the brain in comparison to the liver, and so those studies -- those, sorry, search terms would not have included "acetaminophen."
And I'm trying to recall. There may have been additional cases where I would not have included the term

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"acetaminophen," but yeah.
Q. Did you include search terms about gestation?
A. I don't recall for sure. I included search terms about -- certainly about fetal, embryonic, neurodevelopment. I don't recall if I specifically used the term "gestation." I may have.
Q. Did you use the term "neurodevelopment"?
A. Yes.
Q. How about "lactation"?
A. This case is not -- again, I can't say -- I can't recall for certain. Since this case is not addressing exposure through the mother's milk, I may not have included that term.
Q. You understand that postnatal day 10 is a neonatal period when we're speaking about mice being studied, right?
A. I am not an expert in how animal-mouse neurodevelopment translates to human neurodevelopment. I understand that there are studies in which that claim is made, but I can't assess the claim.

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Q. Did you purposefully avoid mouse-rodent neurodevelopmental studies concerning acetaminophen exposure because you are, quote, not an expert on that topic?

MR. COHEN: Object to form.

A. No, I did not purposefully avoid any of those -- any such studies.

BY MR. JANUSH:

Q. Do you agree that within your report you didn't grade the animal literature studying APAP for neurodevelopmental disorders?

A. In my area of research, that is not common practice.

Q. So you didn't do it, right?

A. I assessed the strength of the data based on common considerations and science. For example, necessary but sufficient, necessary and sufficient, necessary and not sufficient or is -- you -- as a scientist, of course, you always wait as one experiment is better to address this question than another.

So, for example, to me, the ultimate experiment in this case that has

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been done is these studies where they give mice large doses of acetaminophen and look for surrogates of NAPQI formation, such as -- or NAPQI presence, such as acetaminophen-protein adducts, and they find nothing. So to me, I mean, that's an outstanding piece of data.

MR. JANUSH: Move to strike, nonresponsive.

A. As opposed to, for example --

BY MR. JANUSH:

Q. What do you think my question --

MR. COHEN: No, no, no.

MR. JANUSH: I'm going to stop you.

MR. COHEN: No, no. No, no, no. We're not doing this. He gets to finish. You get to ask the next question. Go ahead and finish.

A. As opposed to, for example, asking a question is there CYP2E1 in exosomes based on some speculation that that might contribute to NAPQI formation in the brain; well, the fact is, there's no NAPQI in the

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brain. So the exosome question essentially becomes irrelevant.

I'm happy to discuss it if you'd like, but that's an example that I just wanted to give of how you would weight the data, right, looking at an actual final endpoint rather than some kind of intermediary speculative step.

BY MR. JANUSH:

Q. What was my question?

A. Your question was essentially -- I don't recall the exact --

MR. COHEN: Object. Object. Sorry.

A. I don't recall the exact wording of your question. I think --

BY MR. JANUSH:

Q. I'm just asking for a yes or no: Did you grade animal literature testing for acetaminophen exposure, yes or no?

MR. COHEN: Object to the form.

A. I don't believe it can be answered with a simple yes or no. All scientists, of course, always sort of weigh, evaluate the strength of different pieces of

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evidence against each other.

BY MR. JANUSH:

Q. Within your report, did you grade the animal-rodent literature testing for acetaminophen for neurodevelopmental disorders? Yes or no?

MR. COHEN: Object to the form of the question.

A. I was not asked to address neurodevelopmental disorders or neurodevelopmental endpoints.

BY MR. JANUSH:

Q. I'm going to make you a deal. I'm going to try and ask really crisp, clear questions; and if I get really crisp, clear answers, your day is going to be a lot shorter, okay?

MR. COHEN: Object to the colloquy. Just ask questions, please.

MR. JANUSH: Oh, I am.

BY MR. JANUSH:

Q. Can you point me to an area within your report where you weighed the animal literature studying APAP for neurodevelopmental disorders?

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MR. COHEN: Object to the form.
A. As I've stated, all scientists are always weighing different pieces of literature, different pieces of data against each other.
BY MR. JANUSH:
Q. I'm not asking about all scientists. I'm asking about your report.
You understand you have your report in front of you, right? Is that -- can you look at it?
A. This is my report.
Q. Okay. Can you peel through it and show me where you graded the animal-rodent literature? It's a yes or no. You either can or you can't.
MR. COHEN: Object to the form.
Go ahead.
A. Again, I don't think that it's a yes -- it can be answered quite so simply.
BY MR. JANUSH:
Q. Well, just point me to the page.
A. Again, as I state, throughout my review of the literature, I weighed

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different pieces of evidence against each other, as is the common practice for a scientist.
Q. Do you grade studies when authoring -- when authoring review articles?
A. Again, we weigh -- weigh different pieces of evidence, different pieces of literature against each other.
Q. But in your report, right now, can you point me to any area where you graded animal-rodent literature?
A. Yeah, again, my answer remains the same, that you -- I always evaluate strengths and weaknesses. That's part of a critical evaluation of the literature.
Q. But where is it? That's what I'm asking. Can you show it to me?
A. The -- what I've written in my report is the result of the critical evaluation of the literature.
Q. I'm not asking about what you wrote. Can you show me where you graded the rodent literature?
MR. COHEN: Object to the form.
///

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BY MR. JANUSH:
Q. You can't, right?
A. Throughout preparation of the document, I was always evaluating strengths and weaknesses of different studies and different pieces of data, as is common practice for a scientist.
Q. Including -- including the available animal-rodent literature?
A. The relevant available animal-rodent literature. Again, I was not asked to address neurodevelopmental outcomes.
Q. You were not asked to address neurodevelopmental outcomes?
MR. COHEN: Is that the question?
BY MR. JANUSH:
Q. Is that your testimony?
MR. COHEN: Sorry. Go ahead.
A. Yes. With the caveat that the questions I was asked to address, the plaintiffs' experts have proposed that they are relevant to those types of outcomes.
BY MR. JANUSH:
Q. And so you didn't seek to

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counter the plaintiffs' claims that they are relevant to those types of outcomes because you didn't -- you're not a neurodevelopmental expert, right?
A. I do counter the plaintiffs' claims with respect to the issues that I've outlined in paragraph 4.
Q. Okay. Dr. McGill, if an expert issuing an opinion on general causation selectively picks literature from the scientific landscape and presents the court with what that expert believes the relevant studies demonstrate, would that be a good thing to do or a bad thing to do in fulfilling an expert role?
MR. COHEN: Object to the form.
A. Well, in terms of general causation, that's not what I was asked to address, and I wouldn't consider that -- causation in the sense of epidemiology and genetics and that sort of thing, what factors weigh heavily into clinical outcomes. That's not my expertise.
In general, yeah, you wouldn't want to cherry-pick studies or data.

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BY MR. JANUSH:
Q. Cherry-picking would be bad, right?
MR. COHEN: Object to the form.
A. Yeah, which is one of the issues that I have with at least one of your plaintiffs.
MR. JANUSH: Move to strike the latter part of your answer.
BY MR. JANUSH:
Q. And the reason from a scientific perspective that cherry-picking literature is bad is because it would be a form of a result-driven analysis that undermines principles of the scientific method, right?
MR. COHEN: Object to the form.
A. A result-driven analysis? I mean, the way I would characterize it is that ignoring relevant data is -- could potentially lead to inaccurate conclusions.
BY MR. JANUSH:
Q. And assessing the weight of the literature as we were discussing before, it was part of your methodology that you did not

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disclose in your report, right?
MR. COHEN: Object to the form.
A. Again, it's -- it's a standard practice in my field to -- I mean, that is just the fundamental part of science, that when you are considering claims that are based on or purportedly based on science, you evaluate the strengths and weaknesses of the available data.
BY MR. JANUSH:
Q. I'm not asking what you evaluate as a scientist. I'm addressing your report.
Assessing the weight of the literature was part of your methodology that you did not set forth in your report?
MR. COHEN: Object to the form.
BY MR. JANUSH:
Q. Is that right?
MR. COHEN: Go ahead.
A. Assessing strengths and weaknesses of studies is an intrinsic part of writing a review, any kind of review, including an expert report.
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BY MR. JANUSH:
Q. But assessing the weight of the literature, the strengths and weaknesses of literature, for example, the body of rodent studies addressing developmental neurotoxicology associated with acetaminophen, you didn't evaluate the strengths and weaknesses of most of those studies, right?
MR. COHEN: Object to form.
A. Again, I was not asked to evaluate any neurodevelopmental or behavioral studies, so that's not my goal here.
BY MR. JANUSH:
Q. Even -- even when those neurodevelopmental and behavioral studies concerned acetaminophen; is that right?
MR. COHEN: Object to form.
A. As I've stated, I was not asked to address neurodevelopmental outcomes or neurodevelopmental studies.
BY MR. JANUSH:
Q. What's this case about?
MR. COHEN: Object to form.
A. The issues that I was asked to

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address in this case --
BY MR. JANUSH:
Q. Not what I'm asking.
What do you understand this case is about? Let me ask it differently.
Do you have an understanding that this case is about mothers and parents claiming that pregnant women took acetaminophen, such as Tylenol, during pregnancy and gave birth to children with neurodevelopmental disorders such as ASD, autism spectrum disorder, and ADHD, who were exposed to acetaminophen in utero?
Do you understand that?
A. I understand that the -- at least some of the plaintiffs are claiming that -- basically claiming injury due to -- for their children due to in utero exposure to therapeutic doses of acetaminophen.
Q. In other words, this case is about developmental in utero neurotoxicology, isn't it?
MR. COHEN: Object to form.
A. This case is about the claims of the plaintiffs, right, and your

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plaintiffs' experts proposed, as I laid out in paragraph 4, a few mechanisms by which that might occur. And that's what I was asked to address, so that's what I'm addressing.

BY MR. JANUSH:

Q. Okay. I am going to give you a demonstrative that I'll have our technician pull up on the screen as well. It's marked as Plaintiffs' Exhibit 802.

(Whereupon, Deposition Exhibit P802, Demonstrative Chart, APAP-Rodent DNT Studies in McGill Report, was marked for identification.)

BY MR. JANUSH:

Q. It's a chart -- it's a chart, Dr. McGill, of 26 animal studies that were addressed by Dr. Pearson -- you remember reading Dr. Pearson's report, right?

A. Yes.

Q. And these are all of the rodent literature addressed by Dr. Pearson -- actually, it's 25 lines, not 26. The first lines at the top are Author, Title, Year.

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Column E is Mentioned in McGill Report. Column F is Analyzed in McGill Report. Column G is on McGill Materials Considered List. And column H is whether it's mice or rats.

Do you see that?

MR. COHEN: Just before you continue, Counsel, is this part of Dr. Pearson's report?

MR. JANUSH: No. I said this is a demonstrative that I'm addressing for demonstrative purposes.

MR. COHEN: Okay. Well, just standing objection to the use of demonstratives like this that have been created by lawyers for the purpose of this deposition. We're going to object to this. We're going to object to them being even marked as exhibits and being put on the record as exhibits. This is -- we don't think it's proper, but you can go ahead and ask questions.

BY MR. JANUSH:

Q. Dr. McGill, we show that --

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well, let's look at Beck. You didn't mention Beck in your report, right, Spatial Glutathione and Cysteine Distribution and Chemical Modulation in the Early Organogenesis-Stage Rat Conceptus in Utero?

MR. COHEN: Object to the form of the question.

A. Understand when I answer these questions, I'm relying on your document. Based on this document, I didn't address it.

BY MR. JANUSH:

Q. So we show three rodent studies: At line item 17, the Koehn study; line item 18, the Klein study; and line item 21, the Rigobello study, that you addressed -- mentioned in your report.

Do you see that?

A. Yes.

Q. And then separately, when we look at analyzed in your report, we show those same line items, those same three studies. And then there's a host of studies on your considered list that aren't even present on your considered list, the Beck study, the --

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And by the way, you don't have to trust me. You have your materials considered list in front of you appended to your report. You can feel free to cross-check me. You can open it up and cross-check me. You can tell me if I'm wrong, so feel free to do that.

But we show that you didn't address the Beck study.

You didn't address the Blecharz-Klin study, Effect of Prenatal and Early Life Paracetamol Exposure on the Level of Neurotransmitters in Rats, with a focus on the spinal cord.

You didn't address the Blecharz-Klin study Developmental Exposure to Paracetamol Causes Biochemical Alterations in Medulla Oblongata.

You didn't address Blecharz-Klin Cerebral [sic] Level of Neurotransmitters in Rats Exposed to Paracetamol During Development.

You didn't -- and I say address. "Consider" is the appropriate word, so forgive me -- Philippot at line 19,

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Evaluation of the Dentate Gyrus in Adult Mice Exposed to Acetaminophen on Postnatal Day 10.

Suda, Therapeutic Doses of Acetaminophen with Co-administration of Cysteine and Mannitol During Early Development Result in Long-Term Behavioral Changes in Laboratory Rats.

Didn't address 22, Philippot, Paracetamol (Acetaminophen) and Its Effect on the Developing Mouse Brain.

Didn't address -- or consider, sorry -- as to everything when I'm saying address here, we're on the materials considered list.

You didn't consider Herrington, Elevated Ghrelin Alters the Behavioral Effects of Perinatal Acetaminophen Exposure in Rats.

Didn't address Harshaw, Interleukin-1-beta-Induced Inflammation and Acetaminophen During Infancy: Distinct and Interactive Effects on Social-Emotional and Repetitive Behavior in C57BL/6J mice.

Didn't address Baker, Sex-Specific Neurobehavioral and Prefrontal

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Cortex Gene Expression Alterations --

A. Sorry, you're saying I didn't consider --

Q. Didn't -- sorry --

A. -- it, but if you look at Baker, it does say yes.

Q. Sorry, apologize. That's where you didn't mention it in your report. So you considered Baker but didn't mention Baker in your report, right?

A. I --

MR. COHEN: I'm sorry, was --

MR. JANUSH: In that one.

MR. COHEN: This question now is about one study? Because that was a long, long question.

BY MR. JANUSH:

Q. So now as to -- I actually wasn't asking a question there.

MR. COHEN: Maybe the longest question in the world.

BY MR. JANUSH:

Q. So I'm just reading through this chart and addressing the studies you didn't list on your considered list. You

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appreciate that, right?

A. Based on your evaluation of those materials.

MR. COHEN: Yeah, object to the form.

A. Yes.

BY MR. JANUSH:

Q. So why don't we not base it on my evaluation. Open your report, turn to your materials considered list. Check me. Show me where you considered Beck.

A. What I'd like to point out -- I'm happy to go through these --

Q. I just want you to go through it. And I'm just asking you to tell me --

MR. COHEN: Just answer his questions.

BY MR. JANUSH:

Q. My question is show me where you considered Beck.

A. Beck is not on my materials considered list.

Q. Show me where you considered Dean -- excuse me, not Dean. Blecharz-Klin.

A. There are two. Either one

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you're asking?

Q. Both aren't on your considered list, correct? Well, there's actually more than that. There's -- Effect of Prenatal, the one starting with Effect of Prenatal, Blecharz-Klin. There are five, I think, Blecharz-Klin studies. You considered two; three, you didn't consider.

You can just tell me if you count two.

A. Well, what I can say is that you have two on the list that are not listed in my materials considered list.

Q. Okay.

A. We do have other studies by the same authors though.

Q. I have three, there's another one. Cerebral Level of Neurotransmitters, that's not on your list either, right, by Blecharz-Klin.

A. Can you say the name again, please.

Q. Cerebral Level of Neurotransmitter in Rats Exposed to Paracetamol During Development.

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A. Right. I didn't include them because I'm not looking at cerebral levels of neurotransmitters. That's not what I was asked to address. So I had no reason to consider that literature.

Q. Philippot, can you show me where Evaluation of the Dentate Gyrus in Adult Mice Exposed to Acetaminophen on Postnatal Day 10 was considered?

A. Sorry, which Philippot study are you asking about, Adult Neurobehavioral Alterations?

Q. Evaluation of the Dendrite -- well, I said Evaluation of the Dendrite Gyrus in Adult Mice Exposed to Acetaminophen.

A. Dentate gyrus. Yeah, I cite two other studies with Philippot as the first author. That one is not on the list because I'm -- I was not asked to address anything about the dentate gyrus. It wasn't relevant to the questions I was asked to address, so of course it wasn't in my materials considered.

Q. How about Suda, Therapeutic Doses of Acetaminophen with Co-Administration

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of Cysteine and Mannitol During Early Development Result in Long-Term Behavioral Changes in Laboratory Rats?

Didn't consider that, right?

A. I don't have Suda on my list.

Q. How about Philippot, Paracetamol (Acetaminophen) and its Effect on the Developing Mouse Brain?

Is that on your list?

A. It is not one of the Philippot studies that I cited -- or that I considered, excuse me.

Q. How about Herrington, Elevated Ghrelin Alters the Behavioral Effects of Perinatal Acetaminophen Exposure in Rats?

Is that in your list, Herrington, of considered materials?

A. Herrington. No, again, they're looking at ghrelin levels, not something I was asked to address. There may be studies on my materials considered list that are not directly relevant to the questions that I was asked to address, but that's because I looked at some literature just for background and context of the whole question at hand.

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But there's no reason why I would have a comprehensive evaluation of many studies like this looking at ghrelin or IL-1-beta because those are things that I was not asked to address.

Q. You have dozens of pieces of literature on your materials considered list that have nothing to do with the actual issue you were asked to address though, right?

A. As I stated, I reviewed some additional literature that -- to get context and background for the case overall.

Q. Not just some, dozens, right?

MR. COHEN: He wasn't finished. Please let him finish his answer.

A. So there -- yes, there may be pieces of data, but again, there's no reason why I would have a comprehensive search for additional pieces of data like this, you understand, because these are not what I was asked to address.

BY MR. JANUSH:

Q. Admittedly, I find it interesting that rodent studies were not what you were asked to address, and the reason is

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because it's not easy to test for neurodevelopmental in utero outcomes without turning to animal models, right?

MR. COHEN: Object to form.

A. So to clarify, it's not that I did not include animal studies. We do have animal -- I did consider animal studies in my report. For example, the animal studies that show that massive overdoses of acetaminophen do not cause evidence of NAPQI formation in the brain.

BY MR. JANUSH:

Q. We'll get into that later.

MR. COHEN: Please let him finish.

A. Can you restate the second part of your question? There was something additional I wanted to point out. Oh, that was it.

You were asking about it's difficult to look at effects in utero without using animal models. My response to that would be, well, plaintiffs' experts have relied on many studies that used, for example, cell culture models that also

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absolutely cannot model in utero exposure, among other pieces of data that have no relevance for in utero exposure.

BY MR. JANUSH:

Q. If you were in a hearing before Judge Cote in this case and the judge overseeing this case asked you why you failed to mention in your report 23 of the 26 rodent studies addressed by Dr. Pearson, how would you respond to Judge Cote?

MR. COHEN: Object to the form.

A. As I've already said, these papers are not addressing the issues that I was asked to address, so there's no particular reason why I should have a list -- why I should have included these additional studies.

MR. COHEN: Mr. Janush, at a reasonable point can we take a break? We've been going way over an hour.

MR. JANUSH: We can take a break right now.

MR. COHEN: Whatever is convenient for you.

MR. JANUSH: I can keep going.

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It's your call.

MR. COHEN: Okay. Let's take a break.

THE VIDEOGRAPHER: We're going off the record. The time is 10:04.

(Recess taken, 10:04 a.m. to 10:21 a.m. CDT)

THE VIDEOGRAPHER: We're going back on record. The time is 10:21.

BY MR. JANUSH:

Q. Dr. McGill, when you received your doctor of toxicology and pharmacology at the University of Kansas, who was your research advisor in your doctorate program?

A. Just a point of clarity, my doctorate is in -- technically in toxicology, although as I mentioned, it did include pharmacology training.

My research advisor -- sorry.

Q. What's your doctorate in? I --

A. Toxicology. Sorry, toxicology.

Q. Right. What did I say?

A. You said pharmacology.

Q. Sorry. I meant to say -- sorry -- doctor of toxicology at the

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University of Kansas. Right.

Who was your research advisor?

A. A person named Hartmut Jaeschke.

Q. Hartmut Jaeschke?

A. Correct.

Q. Has Hartmut Jaeschke been a significant mentor in your academic career?

A. He was my PhD mentor. I stayed with him briefly as a postdoc fellow as well.

Q. Have you also published a great deal with Hartmut Jaeschke?

A. I guess it defines [sic] on your definition of a great deal. We have published a number of papers together.

Q. Approximately how many?

A. Oh, boy. Off the top of my head, I don't recall. I would -- I would guess in the ballpark of 60.

Q. Indeed, Professor Jaeschke suggested you should be an expert in this case; is that true?

MR. COHEN: Object to the form.

A. No, he did not. Not to my knowledge, no.

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BY MR. JANUSH:

Q. None of the literature you published with Hartmut Jaeschke concerns the study of acetaminophen and its potential causal nexus with fetal neurodevelopmental disorders, right?

A. I'm sorry, bit of a long question, so I just want to make sure I'm considering it.

Q. I'll shrink it.

Did you study fetal neurodevelopmental disorders with Hartmut Jaeschke that led to publications?

A. Again, my expertise and training are not in neurodevelopment, so no, I've not published on that with Hartmut or otherwise, other than what we've addressed in our review and what we've -- what I've published that's relevant to this -- the questions that I'm considering in this case.

Q. Would you agree that experts should ensure objectivity of their research and publications?

MR. COHEN: Object to form.

A. I -- yeah, I agree that you

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should be as objective as possible. I have to think how to frame this. You're always guided -- well, I shouldn't say guided.

You're always testing a hypothesis, right, and how you -- as I mentioned with the scientific method, you have your hypothesis, you make predictions based on that, and then you test them. You should be objective in your testing and in your evaluation of the results of the testing, yes.

BY MR. JANUSH:

Q. How many scientific publications did you author with Hartmut Jaeschke that were funded by grants from McNeil Pharmaceuticals, the former corporate entity that made and sold Tylenol?

MR. COHEN: Object to form.

Go ahead.

A. So when I was -- I'll start by saying I don't know all of Hartmut's funding history, all the details, right? It didn't -- how to say that -- I was not a recipient of any of those funds, so I guess I have no reason to be familiar with all those

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details.

There were -- as I recall, when I was working in his laboratory, he did have some funding from McNeil, which I -- I believe is a -- basically J&J or associated with J&J. I think there were maybe three, four studies that -- for which Hartmut received some support from that entity.

BY MR. JANUSH:

Q. Okay. You said you wouldn't have reason to know what Hartmut received funding on from McNeil or J&J. Let's turn to your footnote 24, reference citation 85, Exhibit 803. I'm just going to make it easy on you by handing it over to you.

(Whereupon, Deposition Exhibit P803, Plasma and Liver Acetaminophen-Protein Adduct Levels in Mice after Acetaminophen Treatment: Dose-Response, Mechanisms, and Clinical Implications, by McGill et al., was marked for identification.)

BY MR. JANUSH:

Q. This is a publication that you

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are a coauthor on with Hartmut Jaeschke; is that right?

A. Yes.

Q. And if you look at the screen, I've had our technician pull up: This investigation was supported in part by grants from McNeil Consumer Health to HJ and DR.

Do you see that?

MR. COHEN: I'm sorry. What page is that on?

A. Yeah, I --

MR. JANUSH: So the funding acknowledgement is --

MR. COHEN: I found it. Thank you. Page 8.

BY MR. JANUSH:

Q. So do you see that on the screen, this investigation was supported in part by grants from McNeil Consumer Health Inc.?

A. I see that, that it was supported in part by grants from McNeil Consumer Health to Hartmut and Dr. Rollins -- I'm sorry, Dr. Jaeschke and Dr. Rollins.

Q. But when a company like McNeil

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that made and sold Tylenol at that time is sponsoring a coauthor of yours, that aids in the publication getting published, correct?

MR. COHEN: Object to the form.

BY MR. JANUSH:

Q. In other words, grant money helps scientists fund studies, true?

A. Science is an expensive endeavor. It requires funds for sure.

Q. And so in your report, you have an area where you disclose ongoing funding for studies and funding for past studies; is that right?

A. I believe I did.

Q. You don't list this study, right?

A. No, because I did not receive any funding for this study.

Q. So is the standard that you wouldn't list funding because you personally weren't the grant recipient and it was one of your coauthors?

A. Well, may -- can you please tell me the page number in my report --

Q. Sure.

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A. -- that you're looking at.
Q. I think it's --
A. I don't want to waste everybody's time by flipping through here trying to remember where I put it.
Q. I think it's PDF page 113 to 115, so that will help us a bunch on the actual report, Exhibit 801. It's hard to follow your report. It changes pagination.
A. I'm sorry. Yes, right, that's what I was saying, yes.
Q. So it's page 11 of --
A. Page 11?
Q. -- your listed work.
MR. COHEN: I apologize, Counsel. Are you talking about his report or his CV?
MR. JANUSH: Well, his CV is appended to his report. That's how it was served. So it's an appendix to the report.
THE WITNESS: Yeah, I think this is the source of the confusion.
BY MR. JANUSH:
Q. You have -- at page 5, you have

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Research, Journal Publications (latest to earliest).
That's why I think we should go to the screen and pull up P801 and go to page 113, and at PDF page 113, the first reference citation -- well, we can look at -- I believe it's the next page is reference citation 85. And that's the report. That matches the title.
You see that, Plasma and liver acetaminophen-protein adduct levels in mice after acetaminophen treatment?
A. I see it.
Q. So here is a study with Hartmut Jaeschke and you and others addressing plasma and liver acetaminophen-protein adduct levels in mice after acetaminophen treatment sponsored by the makers and sellers of Tylenol, right?
MR. COHEN: Object to the form.
BY MR. JANUSH:
Q. At least sponsored as to your coauthor, Hartmut Jaeschke, correct?
MR. COHEN: Object to the form.
A. Hartmut, Dr. Jaeschke, received

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some funds from McNeil. Again, I point out that I am not a recipient of any of those funds, nor have I ever received, prior to this litigation -- my involvement in this litigation, have never received any sort of funds from J&J.
BY MR. JANUSH:
Q. Let's go to the next reference citation. It's on the page before. It's reference citation 79 and it's Exhibit P804.
(Whereupon, Deposition Exhibit P804, Apoptosis or Necrosis in Acetaminophen-Induced Acute Liver Failure? New Insights From Mechanistic Biomarkers, by McGill et al., was marked for identification.)
BY MR. JANUSH:
Q. Here's the first page of what I was able to get.
MR. COHEN: And just for clarification, Counsel, on the record -- when you say "on the report," you're now looking at his -- and putting up on the screen pages from his curriculum vitae.

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MR. JANUSH: Yes, that is -- was appended as an exhibit to his report.
MR. COHEN: I understand that.
MR. JANUSH: It was served as one document, one PDF, and so that's how I'm referring to it.
BY MR. JANUSH:
Q. And here we're addressing again --
MR. JANUSH: You can go back to where you were, David.
BY MR. JANUSH:
Q. We'll call it on the screen so you can see it easier. Here too is a callout for McNeil funding. Dr. Jaeschke received research grant supports from -- consulted for McNeil Consumer Health, sorry.
Do you see that? Dr. Jaeschke consulted for McNeil Consumer Health with respect to this study?
A. That's not the portion that's highlighted, but I see the statement.
Q. Now it's being highlighted. Do you see that now that it's highlighted?

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A. Yes.
Q. So that's not just grant support. This is your coauthor consulting for McNeil Consumer Health within the confines of this particular publication, right?
MR. COHEN: Object to the form.
BY MR. JANUSH:
Q. That's what that disclosure is, right?
A. No, that's --
MR. COHEN: Object to form.
A. That's an inaccurate statement. In this particular case, there's no statement of research support for this publication.
Dr. Jaeschke -- or my interpretation -- my read of this, based on my career of experience in this field, is that he's just being extra cautious and pointing out, by the way, I've received -- or he has consulted for McNeil Consumer Health.
BY MR. JANUSH:
Q. It's called a conflict of interest disclosure, right?
A. It's a conflict of interest

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disclosure in which you report anything that could be perceived by someone as a potential conflict.
Q. Okay.
A. But again, this is not support for that article, and again, it has nothing to do with me.
Q. Let's go to reference citation 77, Exhibit P805.
(Whereupon, Deposition Exhibit P805, Circulating Acylcarnitines as Biomarkers of Mitochondrial Dysfunction after Acetaminophen Overdose in Mice and Humans, by McGill et al., was marked for identification.)
A. Thank you.
BY MR. JANUSH:
Q. Circulating Acylcarnitines as Biomarkers of Mitochondrial Dysfunction with Acetaminophen Overdose in Mice and Humans. You are a coauthor with Hartmut Jaeschke, amongst others, right?
A. Correct.
Q. And here too, was this also

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supported in part by grants from McNeil Consumer Health to Hartmut Jaeschke and to Steven C. Curry?
And you can look at the screen. I'm trying to speed it along for you.
MR. COHEN: Well, no, he's entitled to look at the --
MR. JANUSH: You are absolutely entitled to look at the document, but we're also calling it up in real time to make it easy for you.
A. I see the -- that the statement says that. Again, grants from McNeil Consumer Health to Hartmut and Dr. Curry apparently.
BY MR. JANUSH:
Q. And we'll go to your footnote 2 from your report, which is also reference citation 94. This is P806.
(Whereupon, Deposition Exhibit P806, The mechanism underlying acetaminophen-induced hepatotoxicity in humans and mice involves mitochondrial damage and nuclear DNA fragmentation, by McGill et al., was

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marked for identification.)
BY MR. JANUSH:
Q. And this is: The mechanism underlying acetaminophen-induced hepatotoxicity in humans and mice involves mitochondrial damage and nuclear DNA fragmentation.
Do you see that?
A. Yes.
Q. And on the very bottom of the first page -- you don't have to go far. You don't have to flip through this one.
A. The first page.
Q. On the bottom left-hand corner, conflict of interest, Steven C. Curry and Hartmut Jaeschke are supported by grants from McNeil Consumer Health.
Do you see that?
A. I see it.
Q. So here too, two of your study authors were funded by the makers and sellers of Tylenol, right?
MR. COHEN: Object to the form.
A. Based on this statement, Dr. Curry and Dr. Jaeschke have received

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grants from McNeil.
BY MR. JANUSH:
Q. Is that a "yes" to my question?
MR. COHEN: Object to form.
A. Well, my answer is that apparently Dr. Curry, as well as Dr. Jaeschke, have received grants from McNeil. That's what the statement says.
BY MR. JANUSH:
Q. Just to be clear, I want to make sure I'm getting this right: Your standard in not disclosing grants from McNeil, the maker and seller of Tylenol under the J&J family of companies, was because you specifically were attenuated from that grant, right? It wasn't monies given to you directly?
A. I'm sorry.
Q. Just to your coauthors, right?
MR. COHEN: Object to the form. Go ahead.
A. Sorry. Where did I not disclose? What are you referring to?
BY MR. JANUSH:
Q. Well --

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A. It is disclosed in these publications.
Q. You have a section in your report, right, and it's entitled -- I'll take you to it. It's at page 20 of your CV.
A. Is this -- okay.
Q. Extramural funding.
A. Yes.
Q. Page 20, starts at the very bottom of page 20, extramural funding, way back like the fourth-to-last page of the entire PDF of your expert report.
A. Yes.
Q. That extramural funding, studies are listed, right?
A. Well, extramural sources of funding for my research are listed.
Q. Right.
A. For research in my laboratory.
Q. Okay. So when -- and then there's another area that addresses intramural funding, right?
A. Yes, I believe there is a section on intramural funding.
Q. But with respect to extramural

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funding for your laboratory, you had no problem listing when you are in the role of, quote, other personnel on a laudatory grant of $4,278,884 from the National Institutes of Health with James as the PI, right? Here, you're not the PI on that, right?
A. Right.
Q. It's at the bottom of page 21. I want to make sure you're looking -- middle of page 21. I want to make sure you're looking at it with me. It's also up on the screen.
A. No, I'm not the PI. "Other personnel" is not a general term. It's an official category with the National Institutes of Health. I'm listed as -- officially listed as -- in that official category of other personnel, and I receive salary support for it.
Q. Okay.
A. So in that sense, I -- this is one of my projects.
Q. And then on the next one, you also had no problem listing -- literally, the very next one, yep, KO1 DK126990, National

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Institutes of Health, Lutkewitte is the PI. I'm sure I'm pronouncing that name wrong, but that's who the PI is on this study with a grant of $521,314, right?
A. That's correct. So again, what is typical to list on your CV is when you are a named individual on that grant. Otherwise, you know, if I were to list myself as a grant on Dr. Jaeschke's McNeil funding -- sorry, list myself as personnel in any capacity on Dr. Jaeschke's McNeil funding, that would be unethical because this is a presentation of my work, and others in my field would see it as me taking some credit for his work.
MR. JANUSH: Move to strike, nonresponsive. I didn't have a question pending for you to answer.
BY MR. JANUSH:
Q. At the bottom of that, I see: Effort, colon, 0% FTE. So on this one, $521,314 grant not provided by McNeil, you had 0% FTE. Explain what FTE is.
A. FTE stands for full-time equivalent.
Q. So what does this mean, 0%

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full-time equivalent?
A. Yeah, so what it means is that I was in an official named capacity on this grant as other personnel, but I declined any salary recovery from it. This was a -- this was a type of training grant, it's a KL1. Dr. Lutkewitte was a postdoc along with myself at Washington University in St. Louis. He obtained this grant as PI, but a component of the grant is mentoring.
And so he asked me, as I was a bit ahead in my career, if I would be willing to mentor him. And I said yes because I believe that's a very important thing to do, mentor young scientists, and I did not feel that I should take any salary recovery from it.
Nevertheless, I was an officially named person in the grant, which is why I've included it in here.
Q. And similarly, when a coauthor gets grant money from the makers and sellers of Tylenol to publish science related to Tylenol and neurotoxic issues, that advances, as a whole, the entire publication, right?

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MR. COHEN: Object to the form.
BY MR. JANUSH:
Q. In other words, when one scientist receives grant money from the maker and seller of Tylenol, that has the benefit of aiding the entire work, right?
MR. COHEN: Object to the form.
A. Again, science is an expensive endeavor. You need funds to do it. There are -- I mean, it helps you to pay for things like pipette tips, tubes, things that are necessary to do -- to complete the project.
It doesn't benefit -- well, with respect to Dr. Jaeschke's funding, I was not a recipient, never benefited me personally, other than helping him pay for the pipette tips that I was using.
BY MR. JANUSH:
Q. Marking 807, Plaintiffs' Exhibit 807.
(Whereupon, Deposition Exhibit P807, Webpage, Johnson & Johnson Acquires McNeil Laboratories, was marked for identification.)
///

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BY MR. JANUSH:
Q. This is a screenshot from Johnson & Johnson, Our Story. The Johnson & Johnson Company Timeline. 1959, Johnson & Johnson acquires McNeil Laboratories. And it says: At the heart of its business -- at the bottom, I'm reading three lines from the bottom -- at the heart of its business was Tylenol, the first aspirin-free pain reliever. Today, Tylenol remains a household name and one of Johnson & Johnson's most popular products.
Do you see that?
A. I see it.
MR. COHEN: Object to the -- just note my objection to the use of this exhibit.
Go ahead.
BY MR. JANUSH:
Q. When you were working on studies that were funded in part by McNeil to one of your coauthors, did you have an appreciation that at that time that it was McNeil, the maker and seller of Tylenol?
MR. COHEN: Object to the form.

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A. As I stated in my previous answer, yeah, I'm aware that McNeil -- I don't know exactly their relationship, but I know -- I think I said earlier, McNeil basically is J&J, so...
BY MR. JANUSH:
Q. I didn't say "at that time" in that prior question, so I modified this question.
A. Okay.
Q. Did you know then, when you were publishing your work, that McNeil was paying Dr. Jaeschke grant money to publish that article with you?
MR. COHEN: Object to the form.
A. I knew Dr. Jaeschke had grant funding from McNeil, and -- and yes, that McNeil was part of Johnson & Johnson.
BY MR. JANUSH:
Q. And that McNeil was the maker and seller of Tylenol?
A. I'm aware, yeah.
Q. And you were aware then too?
A. Yes.
Q. Okay. And --

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A. In the United States.
Q. And while serving as an expert in this case, concerning this all-important product to Johnson & Johnson -- it's one of its most popular products according to the web page -- it didn't occur to you that it might be a wise thing to let Judge Cote and the plaintiffs know that four of your publications with Hartmut Jaeschke were sponsored in part by the defendant?
MR. COHEN: Objection. That's just inappropriate.
MR. JANUSH: You may answer.
A. I never received any funding of any form from McNeil or Johnson & Johnson prior to this, my involvement in this litigation. I can't speak to Hartmut's full funding history. I'm aware he had some funding from McNeil.
BY MR. JANUSH:
Q. Did you know that as recent as 2020, your mentor, your former research advisor in your PhD program, and your coauthor on, as you put it, approximately 60 publications, was communicating with

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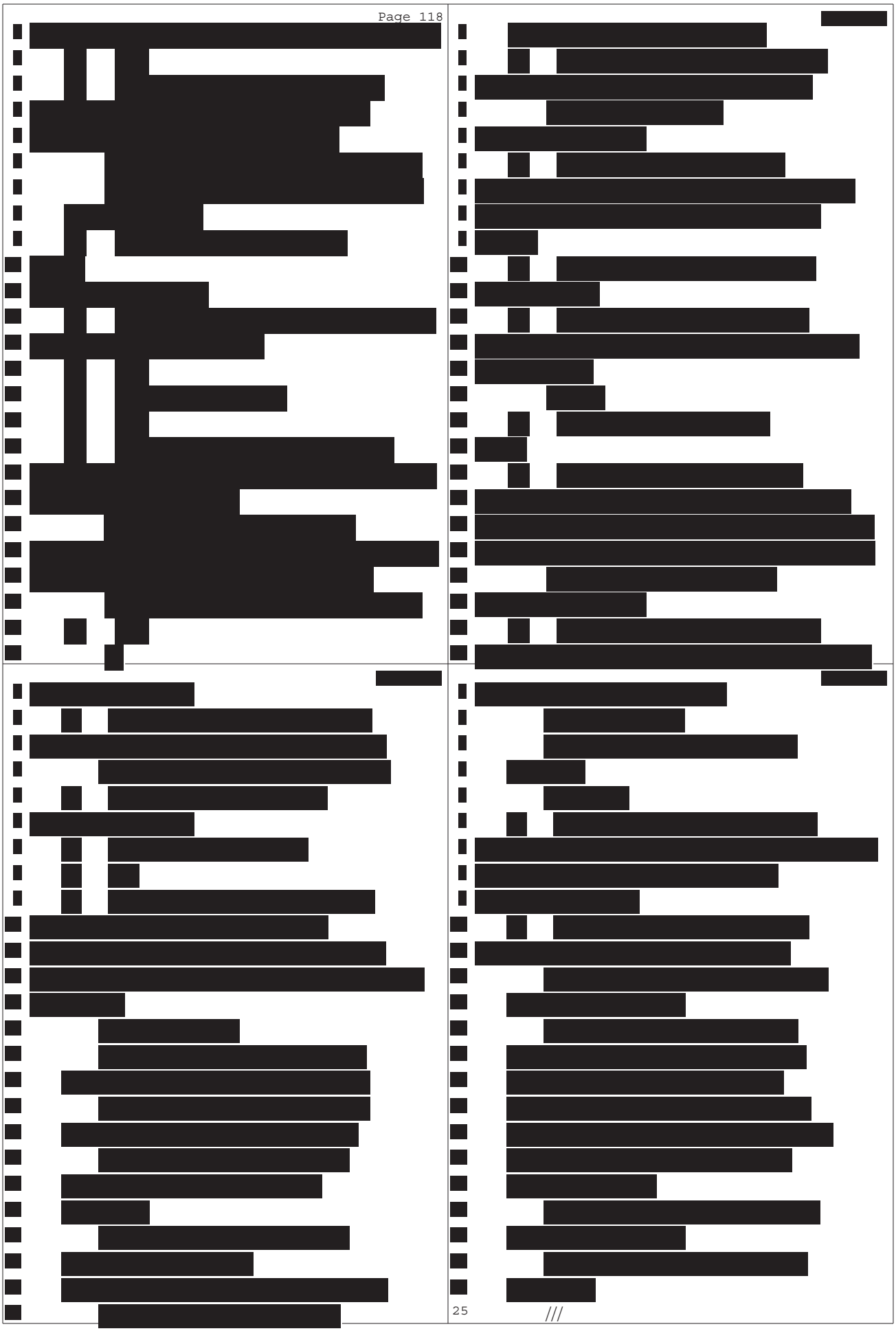
senior -- a senior scientist at Janssen research and development to help the Johnson & Johnson companies counter published literature linking fetal acetaminophen exposure to ADHD?
Did you know that?
MR. COHEN: Objection. Object to the form.
A. No. No, I had no knowledge of that.
BY MR. JANUSH:
Q. Incidentally, do you know how many times you've cited -- let me ask it differently.
Did you know that you cited Dr. Jaeschke within the body of your expert report and the appendices to your report 141 times?
MR. COHEN: Object to the form.
A. Did I know that I did that? No. I mean, I don't know the number of times.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25
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[redacted]

Dr. McGill, I'm going to go through really briefly your summary opinions that are up front in your report that you get into in greater detail later.

So this is at page 6 of the report.

A. It doesn't appear to be page 6.

Q. My apologies.

A. If you're referring to -- I think it was paragraph 4, as we discussed earlier, if that's what you're referring to.

Q. Actually, you know what? I'm

going to do something else.

Dr. McGill, have you reviewed any studies that concluded that biological causation between acetaminophen and fetal exposure -- or between fetal exposure of acetaminophen and neurodevelopmental outcomes are biologically impossible?

MR. COHEN: Object to form.

A. I'm sorry, can you ask the question again.

BY MR. JANUSH:

Q. Have you reviewed any studies concluding that acetaminophen in utero exposure and resulting neurodevelopmental outcomes are biologically impossible?

MR. COHEN: Object to form.

A. So to be clear, I was not asked to address the neurodevelopmental outcomes or anything -- behavioral outcomes, anything similar to that.

What I have reviewed in my literature and stated -- or described in my expert report are a number of studies which together demonstrate that there is no formation of NAPQI in the brain, which is the

question that I was asked to address and that the plaintiffs opine is a mechanism for such neurodevelopmental or behavioral outcomes.

MR. JANUSH: Move to strike as nonresponsive everything after "I was not asked to review -- address the neurodevelopmental outcomes or anything -- behavioral outcomes, anything similar to that." Everything following those words, move to strike.

BY MR. JANUSH:

Q. Dr. McGill, have you made an effort to accurately reflect your understanding of what each scientific piece of literature that you relied on actually addressed in the papers you cited?

A. Yes. The papers that I reviewed in my expert report, I've made my best effort to be accurate.

Q. Because if you inaccurately cite a paper you relied on, it is possible you misunderstood what the paper stood for, right?

MR. COHEN: Object to the form.

///

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BY MR. JANUSH:
Q. Hypothetically.
A. Hypothetically? If -- if one -- I suppose if one summarized a study or described a study incorrectly, it's possible that they misunderstood or missed something.
Q. It's either a misunderstanding or it's a purposeful error, right?
MR. COHEN: Object to the form.
BY MR. JANUSH:
Q. When someone inaccurately cites a paper that they rely on?
MR. COHEN: Object to the --
A. No, it could also just be an honest error that is not the result of misunderstanding, or could be something that's overlooked, some sort of accidental -- so the answer to your question is no.
BY MR. JANUSH:
Q. Let's turn to page 7 -- or excuse me, paragraph 7 of your report. And it's at paragraph 7 that you are addressing different studies you've been involved in focused on acetaminophen, fair?
A. It's describing certain things

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that I considered major foci of my research career that I, you know -- yeah.
Q. And the majority of the studies that are addressed at paragraph 7 concern single-dose overdose of acetaminophen being studied, right?
A. With the caveat that they sometimes involve overdose patients, and overdose patients, it's very difficult to determine what form their overdose took.
Q. And one of the studies that you address concerned whether acetaminophen could cause hearing loss, right? We talked about that earlier?
A. Correct.
Q. And you found that a large single overdose of acetaminophen did not lead to NAPQI formation in the cochlea within the ear of mice, right?
A. Correct.
Q. And by citing to this study, Dr. McGill, were you seeking to imply that an acetaminophen overdose study looking at the cochlea is relevant to the in utero developing fetal brain?

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A. No, I never made such a statement. It is interesting to note that the cochlea contain neurons, and we're talking about the brain, and the parenchymal or major cell type of the brain is neurons, but I never made the statement that you're saying.
Q. And on page 5 in the middle of the page, you address a 2012 publication and you say, quote: In 2012, we published the first evidence that mitochondrial damage also occurs --
Excuse me, I want to read below it. I apologize.
In 2012, we published a comparison of hepatic acetaminophen-protein binding, glutathione and oxidative stress in mice and rats, the latter species being much less susceptible to liver toxicity from acetaminophen overdose. The results indicate that NAPQI must bind to mitochondrial proteins to cause toxicity.
Did I read that right?
A. Yes.
Q. Would you agree that

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mitochondrial dysfunction is critical for the development of necrosis after APAP treatment?
MR. COHEN: Object to form.
A. It's a critical feature of liver injury due to acetaminophen overdose. Specifically, yeah, overdose.
With the caveat that mitochondrial dysfunction is not an irreversible phenomenon. It can occur without subsequent injury.
BY MR. JANUSH:
Q. Now, when we address that paragraph I just read, we see footnote 3 at the end of the sentence, right?
A. Yes.
Q. And here you are citing to your own publication at footnote 3, right?
A. The publication described in that paragraph, yes.
Q. Right.
Did you know, by the way, that you cited to your own publications 12 times within the first 12 pages and within the first 24 citations to your expert report?
A. I wasn't aware of the number,

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but I would like to add that I'm spending much of the first 12 pages describing my career and achievement, so of course I'm going to cite myself.

In addition to that, and again in response to your question previously about how many times I've cited Dr. Jaeschke, acetaminophen toxicity is a relatively small field. There are only a handful of experts. Dr. Jaeschke is one of the leading experts. I am also one of the leading experts. It's difficult not to cite our -- my studies or his studies.

Q. If you're studying the liver, that's right, right? Correct?

A. We don't know that much about -- well, let me rephrase that.

Toxicity in the liver, as well as the kidney, those are the only two well-characterized toxicities of acetaminophen. And so -- I'm trying to consider the best way to say this.

So the majority of research on acetaminophen metabolism and toxicity has been done in the liver, and so due to the

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paucity of data with other potential organ toxicities, we have to rely on that, and, in fact, the plaintiffs' experts also rely on that when they proposed this idea that NAPQI mediates the toxicity in the brain and oxidative stress mediates the toxicity in the brain. So we all have to rely on it just as your experts did.

MR. JANUSH: Move to strike, nonresponsive.

BY MR. JANUSH:

Q. You are a liver researcher primarily, right?

MR. COHEN: Object to form.

BY MR. JANUSH:

Q. Just asking if -- background information. It's a yes or a no.

A. The focus of my research is threefold. So I study various aspects of acetaminophen toxicity with a focus on hepatotoxicity. I also study biomarkers of drug-induced liver injury, including acetaminophen toxicity, and we also look at liver regeneration and repair after injury, including after acetaminophen toxicity.

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Q. How did you arrive at the conclusion that NAPQI, quote, must bind, quote, to mitochondrial proteins to cause toxicity?

A. Yes, so there are multiple sources of data for this, if you'd like me to go into detail. So this idea originated from older data from like 1980s, 1990s. There's a regioisoform of acetaminophen that does not cause liver injury in some models called AMAP. That's -- so what has been observed is that AMAP binds to proteins but does not cause liver injury, and it's thought that that's because if you compare what proteins are bound between acetaminophen and AMAP in some models, the NAPQI from acetaminophen, reacting metabolite of acetaminophen, binds specifically -- or binds more to mitochondrial proteins. The reactive metabolite of AMAP binds less to mitochondrial proteins.

So that was kind of the initial clue that it is probably mediated in part by mitochondrial protein binding.

In addition to that, there are

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other models. For example, this paper in this paragraph that you mentioned, footnote 3 on page 5 of my report, in that paper we demonstrated that rats, which again, are very resistant to acetaminophen hepatotoxicity, have much lower mitochondrial protein binding after an overdose of acetaminophen compared to mice, which are sensitive to acetaminophen hepatotoxicity.

In addition to that, if you block NAPQI formation using P450 inhibitors, then you don't get mitochondrial dysfunction.

So those are three keys pieces of data that contribute probably the most to that statement, that underlie that statement. There are some additional pieces of data as well.

MR. JANUSH: I'm going to mark what's been -- I'm providing what's been marked as Plaintiffs' Exhibit 809.

(Whereupon, Deposition Exhibit P809, Acetaminophen-induced Liver Injury in Rats and Mice: Comparison of Protein Adducts,

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Mitochondrial Dysfunction, and Oxidative Stress in the Mechanism of Toxicity, by McGill et al., was marked for identification.)

BY MR. JANUSH:

Q. And this is a -- the study that you cite in your report at footnote 3.

Do you see that? Can you confirm that? Acetaminophen-induced liver injury in rats and mice?

A. Yes, that's the reference.

Q. And here you are again publishing here with Dr. Hartmut Jaeschke, right?

A. Correct.

Q. And it's 2012.

A. I believe that was the year it was published, yes.

Q. And if we turn to page 4 of 19, we see a statement: Mitochondrial dysfunction is known to play a role in APAP hepatotoxicity in both mice and humans.

A. Uh-huh. I'm sorry, can you tell me -- show me where you're looking at?

MR. JANUSH: Yeah, I'll have

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David search. It's right here under -- there you are, David. You're there.

A. Oh. Yes.

BY MR. JANUSH:

Q. And then after that statement, it says: It is well-established that NAPQI binds to mitochondrial proteins, citing to Tirmenstein and Nelson 1989.

A. Uh-huh.

Q. And it is generally accepted that this is an important early event in the mitochondrial dysfunction and associated oxidative stress seen after APAP overdose.

A. Uh-huh.

Q. Did I read that correctly?

A. Yes.

Q. And you believe in that today, right?

A. With the caveat that in this paper we're talking about the liver.

Q. And if we turn to page 6 of 19 and search for the terms "protein binding, especially mitochondrial protein binding, is necessary for initiation of APAP toxicity" --

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MR. JANUSH: No, not there, David -- Michael. Sorry. I thought this was prehighlighted. I'll find it. It's at the bottom of the page, last paragraph. Protein binding, especially mitochondrial protein binding, is necessary for initiation of APAP toxicity.

BY MR. JANUSH:

Q. Do you see that?

A. I see it, yes.

Q. Do you hold that opinion today?

A. That is what is known to -- it's known that protein binding in the liver after an overdose, and particularly mitochondrial protein binding in the liver after an overdose, is necessary for initiation of APAP toxicity.

APAP being acetaminophen, just for the record.

Q. By the way, just while we're talking about for the record. For the record, the liver has the ability to regenerate. The brain does not have the ability to regenerate following injury,

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right?

A. I -- again, I'm not a neuroscientist. I can't comment on brain regeneration. I have no reason -- well, yeah, I can't comment on brain regeneration. I don't know.

Q. And all these studies that we are addressing in the beginning of your report at page 5 and thereafter, these are looking at liver cells, not brain cells, right?

A. Okay. Can you -- I want to make sure, because --

Q. Page 5, page 6.

A. You're referring to all these studies in my report?

Q. Other -- other than -- other than the cochlea study we've spoken about from 2015, I'm talking about page 5, the 2018 research group addressing liver tissue at the bottom of page 6.

A. Uh-huh.

Q. Liver studies, right?

MR. COHEN: So you want him to check his footnotes; is that what

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you're asking him?
MR. JANUSH: Nope. Nope. He writes it in the body of the text.
If he needs help, he'll let me know.
BY MR. JANUSH:
Q. It says liver.
A. You're asking specifically pages 5 and 6, because there's some additional on page --
Q. I'll walk you there on that. I'm talking about pages 5 and 6, the beginning of your report here.
These are liver studies, right, except for the cochlea study?
MR. COHEN: Object to the form.
Just take your time and review what he's asked you to review.
BY MR. JANUSH:
Q. I didn't ask you to review anything. These are liver studies, right, that you're addressing --
MR. COHEN: You're asking a question based upon all of these studies.

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A. So not exactly. So again, there are actually two studies citing -- one is the hearing loss study.
BY MR. JANUSH:
Q. It says that, yeah.
A. Another is drug metabolism in the ear. So those are two studies. On pages 5 and 6 the rest are dealing primarily with liver injury, though I note on page 7 we mention our review that --
Q. And on page 7, the top two studies that are bulleted, those are also liver studies, right?
A. The top two studies are primarily concerned with liver injury and repair, yeah.
Q. Okay. At page 5 of your report, when you address the bullet: In 2013, we published a study of the dose-response and kinetics of NAPQI formation in the liver in mice, comparing hepatic glutathione and hepatic and serum acetaminophen-protein adducts with various liver damage endpoints. The data demonstrate that NAPQI formation correlates with liver

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injury.
You wrote that, right?
A. Yes.
[redacted]
A. Did we already have -- I guess --
Q. It's 803. I believe I put that before you already. Can you pull that up?
A. Yeah.
Q. Great.
In this study, you address that toxicities might arise at doses below hepatotoxic levels, true?
A. No.
Q. Well, let's look at the abstract in the -- just in the abstract alone, we will look at the following language: Importantly, the data confirm -- it's in the middle, slightly down from there -- importantly, the data confirm

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earlier work that showed that protein-derived APAP-cysteine can appear in plasma without liver injury.
Do you see that?
A. Yes. But protein adduct formation is not toxicity, and you asked about toxicity.
Q. Protein adduct formation is the precursor to NAPQI, isn't it?
A. It's not a precursor to NAPQI, no. NAPQI is formed by P450s and then reacts with proteins. NAPQI is the precursor to protein binding.
Q. So if NAPQI is the precursor to protein binding, and here you're showing protein-derived APAP-cysteine can appear in plasma without liver injury, you're showing that -- you're showing that protein binding can occur without glutathione depletion in this study, right?
A. So to answer your question directly, let me -- what we show in the paper is that protein binding can occur without toxicity.
If you look at Figure 2A,

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Figure 2 on page 15 of the version that I have that you've provided. I'll just give you a moment.

Q. Can you pull that up on the screen? There, it's up on the screen.

A. Okay. Let me know when I can continue, please. Okay.

Yeah, if you look at panel A there in Figure 2, this is total glutathione in the liver, so GSH plus GSSG, because it exists in two forms, so the total is a combination of both. You can see that every single dose we tested caused loss of glutathione.

Q. If we go to page 2, what I want to address, following the introduction in the second paragraph, it says: Forty years ago, a series of critical papers established the mechanism of APAP-induced liver injury begins with the P450-catalyzed conversion of the drug to an electrophile that can react with glutathione, GSH, and bind to proteins.

A. Uh-huh.

Q. This reactive metabolite is generally believed to be

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N-acetyl-p-benzoquinone imine, NAPQI.

It is now thought that binding to proteins, mitochondrial proteins in particular, causes oxidative stress and mitochondrial damage resulting in necrotic cell death.

You wrote that, right?

A. Yes. This is what we call, as I mentioned previously when we were discussing my methodology and how I weigh or compare studies, this is -- protein binding is an event that we would consider in science necessary but not sufficient.

You can have protein binding without toxicity. So in other words, you have to have protein binding to get toxicity in the liver, and -- but it's not enough. It's not enough just to have some protein adducts.

Q. And if we go to page 5. Mechanisms of the appearance of APAP-protein adducts in plasma, you wrote: We have hypothesized that the appearance of APAP-protein adducts in plasma occurs in one of two ways. Protein binding may take place

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exclusively within hepatocytes, followed by secretion or exocytosis of some of the adducted proteins into plasma.

Alternatively, NAPQI could diffuse out of the hepatocyte and bind to plasma proteins in situ. We decided to take an in vitro approach to test these hypotheses.

Did I read that correctly?

A. Yes, those were the hypotheses that we had at the time.

Q. And then when we get to page 7, you address: It has long been believed that G -- extensive GSH -- that's glutathione, right?

A. Correct.

Q. -- depletion is required for protein binding to occur after APAP. Dose-response data supporting this were first published 40 years ago.

And then you go on to say: However, more recent work has challenged this idea. Protein adducts could be measured in human HepaRG cells as early as one hour after treatment with APAP, well before any

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appreciable loss of glutathione had occurred.

And you cite to yourself from 2011, right?

A. Yes.

Q. Moreover, protein-derived APAP-CYS could be detected in serum from humans after only therapeutic doses, citing to Heard 2011.

Do you see that?

A. Yes.

Q. Where in your report did you address that protein-derived APAP-CYS could be detected in humans from only therapeutic doses?

A. So it wasn't really relevant to my report for the reason being that it's most likely -- since the liver is the primary site of drug metabolism, it's most likely that all circulating acetaminophen-protein adducts come from the liver. There's no reason to believe it comes from the brain at all.

So this observation is not really relevant to what we're talking about. And again, protein binding is necessary but not sufficient for toxicity.

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Q. Protein binding is what?
A. Necessary but not sufficient for toxicity. So seeing protein binding is not an indication of toxicity. It's a necessary thing; you have to see it in the liver after overdose, and that's what the plaintiffs opine would happen in the brain as well. So it's a necessary thing. But just having some doesn't mean you get toxicity.
And again, yeah, these are probably mostly coming from the liver since that is the major site of drug metabolism, including acetaminophen metabolism.
Q. And when you say for toxicity, you can only speak to for liver toxicity, right?
A. So when I say toxicity, toxicity occurs with -- is known -- established to occur with acetaminophen overdose in the liver and in some patients in the kidney. So that's what most of our statements and research have focused on.
Q. You're aware, though, of protein binding occurring in other tissue matter, right?

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A. We have provided a little bit of data that there might be some in the lung.
Q. I'm not talking about you personally, your studies.
A. Right.
Q. You are personally aware as a scientist that protein adduct binding occurs in the brain, right?
A. Absolutely not. No, no. There are no acetaminophen-protein adducts detected in the brain by anyone who's attempted to measure it, even after massive overdoses of acetaminophen.
Q. We're going to go through the brain a little more later on and address your brain studies to address the relevancy of what you have set forth in your expert report.
And then further on here at page 7: Our results show that the peak of protein adduct formation in the liver is reached by half hour -- a half to one hour after administration of subtoxic doses and that adduct concentration decreases thereafter.

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Importantly, we were able to detect protein binding after treatment with 15 milligrams per kilogram APAP at these earlier time points, with only a minimal loss of liver GSH. Together, it is clear from these studies that some protein binding can occur without extensive GSH depletion and without toxicity.
Do you see that?
A. I see that. I would also like to note "minimal" is a relative term, right? At the other doses, we also see almost complete glutathione depletion. At the 15-milligram per kilogram dose, if you look at panel A of Figure 2, there was still loss of glutathione, as I said before.
Q. What did you do -- let me ask you something.
Do you believe that the question of babies in utero being protected from a potential harmful toxic product is a serious concern?
MR. COHEN: Object to the form.
BY MR. JANUSH:
Q. In other words, to study that,

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it's important to study it because it's a -- it's an in utero baby that we're talking about, right?
MR. COHEN: Same objection.
A. It's important to -- it would be -- if you're concerned that in utero exposure to some chemical might have adverse effects on the offspring, that's an important concern and it's worth studying.
BY MR. JANUSH:
Q. From a perspective of methodology, what did you do in this case, when considering that Tylenol is a drug that can be taken repeatedly at therapeutic doses over consecutive days by a pregnant woman, to determine what the impact of that minimal protein binding that you spoke of earlier would be over time when glutathione is not being completely depleted?
MR. COHEN: Object to form.
BY MR. JANUSH:
Q. What did you do to rule in or rule out what the impact of that concern is?
A. Well, that's not what I was asked to address, right. I mean, these

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clinical outcomes, it's not -- I'm not an epidemiologist. I'm -- I'm not a physician. I wasn't asked to address --

Q. I'm not talking about the epidemiology. I'm talking about causation. I'm talking about the fact that you are a scientist that studies primarily, from all your publications that I've seen and from what you acknowledge today, liver toxicity, and primarily within the field of liver toxicity, single-dose overdose analysis.

So I'm asking: In a case like this, where we are undoubtedly not addressing single-dose overdoses of Tylenol but, rather, cumulative doses, what did you do to satisfy your safety concern for babies that -- and ensure that your opinion is valid for the women, the pregnant mother who's taking Tylenol repeatedly, day after day during her pregnancy?

What did you do to eliminate a concern that protein binding with minimal loss of liver GSH wouldn't be harmful to a baby?

MR. COHEN: Object to form.

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Go ahead.

A. That's a very long question. First of all --

BY MR. JANUSH:

Q. It is, and I can break it down, but I'm trying to tell a story with you because --

A. I'm prepared to answer the question.

Q. Okay. Good.

A. So, first of all, it's a bit strange to me that you're sort of harping on the single-dose overdose when your own plaintiffs' experts relied extensively on data from studies that use single doses.

In addition to that, when you're talking about, you know, what did I do, well -- to assuage my concern that there might be an effect on the child, well, first of all, there are no data on acetaminophen-protein binding in the fetal brain after maternal ingestion of therapeutic doses of acetaminophen.

The only data that we have on acetaminophen-protein binding in the brain

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comes from rodent studies where they gave massive overdoses of acetaminophen and failed to detect any evidence of protein binding.

So if massive overdoses don't cause NAPQI formation in the brain, I'm not too worried about it at therapeutic overdoses.

Q. And we're going to get to what you consider massive overdoses.

MR. COHEN: If you're at a convenient spot, we've been going over an hour again. Can we take a break?

MR. JANUSH: Sure.

MR. COHEN: Thanks.

THE VIDEOGRAPHER: We are going off record. The time is 11:26.

(Recess taken, 11:26 a.m. to 12:25 p.m. CDT)

THE VIDEOGRAPHER: We are going back on record. Time is 12:25.

BY MR. JANUSH:

Q. Dr. McGill, earlier before we broke for lunch, we had talked a bit about the paper you wrote with Stefanie Kennon-McGill. That's your wife, right?

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A. She's my wife and colleague.

Q. Okay. So that, we're marking Extrahepatic toxicity of acetaminophen critical evaluation of the evidence and proposed mechanisms, by Kennon-McGill et al. as Plaintiffs' Exhibit 839 and handing it to you.

(Whereupon, Deposition Exhibit P839, Extrahepatic toxicity of acetaminophen: critical evaluation of the evidence and proposed mechanisms, by Kennon-McGill et al., was marked for identification.)

BY MR. JANUSH:

Q. And this is from the Journal of Clinical and Translational Research, Extrahepatic toxicity of acetaminophen: critical evaluation of the evidence and proposed mechanisms.

This is the review paper that you did, right? This isn't original science; it's just original summary of literature from your perspective, right?

A. Just a point of clarity. You referred to it as the review paper. I've

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written more than one review but --
Q. The one we discussed though.
A. The one we discussed earlier, it is that paper.
With regard to the question of it does not represent original experimental research, but again, when you write a review like this, you try to critically evaluate the data in the literature, so it's still a critical analysis.
Q. And this was published in 2017; is that correct?
A. That's correct. That's what it lists on the article info.
Q. Okay.
A. It came -- yeah, that's fine.
Q. And right now, we're going to focus on, for the moment, the abstract where it says "relevance for patients."
Do you see that?
A. Yes.
Q. And on the third line down, it says: Recent studies have suggested that APAP can damage cells in other organs as well.

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How can APAP damage cells in other organs as well?
A. So to be clear, what we're saying there is just pointing out that there has -- concerns have been raised about this possibility, so we're not promoting that statement, which is why we used the word "suggested."
Now, in terms of how it can promote -- how it could promote toxicity in other organs, while the --
Q. Let me actually make it easier.
What other organs are we talking about that APAP can -- that it has been suggested that APAP can damage cells within?
MR. COHEN: Object to the form. He was interrupted.
Go ahead.
A. So what we discuss here in the paper -- we can go through it section by section, if you'd like. You can -- Section 2 is about -- is background essentially. Section 3 is about nephrotoxicity, so this is -- we're looking -- addressing the issue

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of toxicity in the kidney. Section 4 is about pulmonary toxicity. There have been claims that there may be some pulmonary toxicity of acetaminophen, at least -- and so we tried to address that here.
There have been claims regarding endocrine disruption and sexual effects on -- excuse me, effects on -- well, effects on the endocrine system and sexual development. There have been claims of ototoxicity, so that's hearing loss, damage in the ear.
And then we finally addressed -- well, not finally, but claims of neurodevelopmental, neurobehavioral disorders.
BY MR. JANUSH:
Q. So earlier when we spoke, early on in this deposition you addressed that you aren't the expert on neurodevelopmental disorders, right?
A. I am not an expert on neurodevelopmental disorders, correct.
Q. And you also discussed that you are not an expert on epidemiology, correct?

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A. I'm not an epidemiologist, correct.
Q. What led you to undertake a scientific review to address neurodevelopmental and neurobehavioral disorders and assess literature and weigh in on this topic as someone who's admittedly not an expert in this field?
A. Right. A couple of things. So, first of all, this is not -- this paper is not a review of the neurodevelopmental claims; this section of the paper is. Just a point of clarity.
The other issue -- another issue is, actually, my wife is a neuroscientist, and she actually did her postdoctoral research on autism spectrum disorders, and we wrote this together.
And in addition to that, in terms of some of the other aspects, such as epidemiological studies, we were careful to cite -- you know, when some of these epidemiological claims came out, there were a number of letters to the editor and editorial comments published in the same journals or

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some different journals by people who have greater expertise and experience in epidemiology than I, and we've cited some of those documents for those specific concerns that we've listed. And so I'm kind of channeling those experts.

Q. So did your wife take the laboring oar on the topic concerning Section 7, Neurodevelopmental and neurobehavioral disorders, when drafting this piece of literature?

A. I'm sorry, I'm not familiar with the term -- what was it? The "laboring oar"?

Q. In other words, did your wife carry the water, do the majority of the writing and research regarding neurodevelopmental and neurobehavioral disorders when addressing Section 7 of this journal?

A. I don't remember the exact proportion of who wrote what. I mean, there's some material in here about sulfation and -- and glucuronidation.

THE WITNESS: Sorry about that,

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I'll try to keep that in mind.

A. So questions of acetaminophen metabolism, and so I most likely wrote that. With regard to some of the other materials, she most likely contributed a great deal.

But again, this is -- we wrote this in 2017, six years ago, so I don't recall the exact proportions.

BY MR. JANUSH:

Q. Okay. And at the last sentence on the first page of the abstract it says: It is especially important to view claims of developmental effects of antenatal APAP exposure with a critical eye because APAP is currently the only over the counter medication recommended for pregnant women to self-treat pain and fever.

Did I read that correctly?

A. Yes, you read it correctly.

Q. And if we flip to the very last page, and we'll start at the top of the left-hand column, its -- it reads, on the fourth line down: Typically, pregnant women are advised not to use NSAIDs due to the increased risk of birth defects and

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miscarriage that has been reported in a few studies. As a result, most pregnant women rely on APAP to control fever and pain. If it can be shown that APAP also poses a significant risk of congenital abnormalities, then that may result in removal of the only remaining treatment option for those patients.

Did I read that correctly?

A. Yes, you read it correctly.

Q. Did either you -- were you or your wife, or collectively both of you, concerned that if acetaminophen could be shown to be related to specific neurodevelopmental disorders such as ASD or ADD or ADHD, that Tylenol could -- could be removed as an option for pregnant women?

MR. COHEN: Objection, form.

A. I'm sorry, it's kind of a long question. Would you mind --

BY MR. JANUSH:

Q. Were you concerned, in writing this review and researching Tylenol and acetaminophen and its potential impacts on pregnant women and their in utero babies,

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that if scientists who are claiming that ADD and ADHD is caused by the drug, that this drug wouldn't be available to pregnant women?

MR. COHEN: Objection, form.

A. I'm not entirely sure I understand. I think I understand what you're asking.

BY MR. JANUSH:

Q. In other words --

A. So --

Q. Let me phrase it differently.

Why -- why were -- wasn't your primary concern the question of protecting the fetus as opposed to what drug is available to treat a -- to treat pain?

A. I mean, this is a very broad -- you're getting into issues of ethics and that sort of thing. I don't know that I would say it was -- I mean, there are two issues to consider here, right, the benefit of the mother, which there's a clear benefit to the mother for using acetaminophen, right?

Again, the -- it's the only drug available -- generally speaking, the only drug recommended for pregnant women to

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use to control pain and fever. So there's a clear, well-established, significant benefit.

If you balance that with the risk of the -- any potential harm to the fetus, well, then you'd better have very good data to justify removing that treatment, the last treatment for the mother.

And our summary here, our analysis of these literature was just that you don't have very good data in support of that concern.

Q. And this is 2017. What did you do, if anything, since 2017? Did you and your wife endeavor to research all of the literature that has developed since then before being retained as an expert since this subject had interested you?

A. So in the intervening years, I've maintained what I would say is a passing interest in the topic. I've tried to stay up on some of the literature, but not in great detail, other than what I've been asked to address in this case.

The reason for that, if you care to know, is -- right, we're just busy

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with other projects, funded projects, and things that are funded by a sponsor take priority because we have to complete those to satisfy the sponsor.

Q. And because it's not your primary area of study interest for which you are sponsored, right?

A. We don't have any grants or funding specifically for this topic.

Q. Did you ever apply for grants or funding specifically for this topic?

A. I have not yet.

Q. Are you going to?

A. I can't say for sure. Yeah.

Q. And I'm going to have Michael search for me for a section called Relevance for Patients.

A. I -- I believe that's in the abstract.

Q. Oh, there it is. Yes. Okay. So we were addressing that earlier.

A. Yes.

Q. Is this section devoted to information that might be clinically relevant for people taking or recommending

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acetaminophen?

A. This is a section that's required by this particular journal, and so yes, they ask you to comment on things that might be relevant for patients. That's why it says Relevance for Patients.

Q. So to summarize, let's talk about some of the tissues in the body that acetaminophen affects that you've addressed in this journal publication.

You agree it affects the liver, right?

MR. COHEN: Object to form.

A. Well, I agree that overdose causes liver injury.

BY MR. JANUSH:

Q. You agree that acetaminophen affects kidneys, right?

MR. COHEN: Object to form.

A. Acetaminophen overdose causes kidney injury in some patients.

BY MR. JANUSH:

Q. You agree that acetaminophen affects lungs, right?

MR. COHEN: Object to form.

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A. It's quite a bit more controversial. I'd say it's not well established. There's no evidence of overt lung toxicity. Some concerns have been raised by other people.

BY MR. JANUSH:

Q. And you agree, including you've published on it, that acetaminophen -- well, you agree that acetaminophen can affect the ears as well, right?

MR. COHEN: Object to form.

A. No. Well, we -- the conclusion from that -- our conclusion from the data that we obtained from that study and from some related studies was that there is no ototoxicity, even with large overdoses.

BY MR. JANUSH:

Q. But you found -- I'll move on to the next question.

Dr. McGill, in this paper you say that no mechanistic studies had been performed on the relationship between acetaminophen and neurodevelopment, right?

A. I --

MR. COHEN: Object to form.

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A. Can you point me to where --
MR. COHEN: Yeah, go ahead.
A. Can you point me to where I state that?
BY MR. JANUSH:
Q. Yeah, it's in the section on neurodevelopmental disorders.
No mechanistic -- last page, Biological relevance and future studies. Third line of the last paragraph on the left-hand side: No mechanistic studies have been performed, and the few mechanisms that have been proposed have not been directly tested.
A. That's the statement that I made at the time that we wrote this.
Q. At that time, how did you come to that conclusion? Did you perform a literature search?
A. Yes.
Q. And were you unaware of the Viberg paper that was done in 2014?
A. I can't say what I was aware of or not aware of at that time.
Q. But you apparently didn't find

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it in your literature search, right?
A. I don't know. You'd have to -- I may have found it and deemed it irrelevant. I don't know. I'd have to see the paper, and even if I saw the paper, I don't know what I was thinking six years ago or seven years ago when we actually wrote it.
Q. When you addressed that conflicting epidemiological studies exist, what conflicting epidemiological studies were you referring to in this paragraph?
A. So I'll tread carefully here because, again, I'm not an epidemiologist, but for -- if you'll just give me a moment.
(Document review.)
A. So, for example, on the prior page, 303, the right column near the bottom, we stated here -- this is with -- I think this section is -- I haven't had a chance to reread it all in detail. I think in the section we're referring to ADHD, and we just noted that it seemed like there was at least one study -- so we say -- state specifically: Interestingly, one group has even tested the association between prenatal acetaminophen

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and ADD/ADHD-like behavior in mice and found no evidence to support it.
And I believe, if I can have a moment to look through it again...
(Document review.)
A. I mean -- so understanding that we wrote this, yeah, six years ago at least, and -- and I haven't had time to review the entire document, I guess I was referring to that study that I just mentioned where I quoted from.
BY MR. JANUSH:
Q. Did you do a Bradford Hill analysis when addressing the, quote, conflicting, quote, epidemiological studies you referred to in this journal review?
A. Again, so I'm not an epidemiologist, and doing -- using the Bradford Hill criteria is not standard in my -- in my area of research.
What we did do, again, as I stated earlier, is cited experts, people who have more expertise in patient care or epidemiology than I, and just to describe some of the concerns that they have raised.

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Q. But just to even write a statement like: No mechanistic studies have been performed, and the few mechanisms that have been proposed have not been directly tested. In fact, there is strong evidence that ASD, in particular, is driven by genetics, so exposure to APAP or other xenobiotics may not be important.
And then you get into: Males are more likely to develop ASD, and siblings of children with ASD are at greater risk, period.
And so these are weighty scientific conclusions that you are drawing as someone who's not an epidemiologist. How did you feel qualified to even write this piece of literature here at that paragraph at Section 7?
MR. COHEN: Objection, form.
A. As I stated earlier, with regard to ASD, my wife is a neuroscientist and did her postdoctoral research in ASD. So this was -- as I recall, this was one of her contributions, particularly the genetic -- the role of genetics and so on.

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Again, other people with expertise in epidemiology, I mean, as you've seen, other defense expert reports have raised significant concerns about biases and confounding in the epidemiological studies.

The best I can do is channel their opinions when it comes to epidemiology, and so that's what we did with the opinions that we saw at the time.

BY MR. JANUSH:

Q. Okay. I'm going to go back to your report. We're going to turn to page 19 -- sorry, page 9, paragraph 19, where I'm addressing your language, quote: It is critical that any experimental model of therapeutic acetaminophen exposure mimics these concentrations and durations. And you're speaking about concentrations you addressed in paragraph 18.

A. Uh-huh.

Q. A model that results in substantially higher concentrations or exposure to acetaminophen for inappropriate lengths of time cannot be said to model therapeutic use in humans.

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And here's where I'd like to focus the next two sentences: Although it is tempting to refer to any sub-hepatotoxic dose or concentration of acetaminophen as therapeutic, that is incorrect. The terms "therapeutic" and "sub-hepatotoxic" are not interchangeable.

You wrote that, right?

A. Yes.

Q. Do you believe in that today still?

A. Absolutely.

Q. Okay. You go on to address rats and how they're highly resistant to the hepatotoxic effects of acetaminophen, right?

A. Yes. I also -- sorry.

Q. First I want to address your statement that the terms "therapeutic" and "sub-hepatotoxic" are not interchangeable. That's wrong, isn't it?

A. Absolutely not.

Q. Have you stated the opposite in published literature?

A. No.

Q. No? Okay.

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Do you remember publishing an article with Hu and Jaeschke called Low-dose Acetaminophen Induces Reversible Mitochondrial Dysfunction Associated with Transient c-Jun N-terminal Kinase Activation in Mouse Liver in 2016?

A. Sure do.

Q. Okay. We've marked that as P837.

(Whereupon, Deposition Exhibit P837, Low-Dose Acetaminophen Induces Reversible Mitochondrial Dysfunction associated with Transient c-Jun N-Terminal Kinase Activation in Mouse Liver, by Hu et al., was marked for identification.)

BY MR. JANUSH:

Q. Let's go -- first page, 204, bottom of the left side under the bold black line: APAP toxicity shows a threshold dose-dependence such that therapeutic doses are generally considered nontoxic.

Did I read that correctly?

A. Yes.

Q. That's the exact opposite of

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what you wrote at paragraph 19, page 9, isn't it?

A. No.

Q. Well, let's look at paragraph 18, page 9 -- paragraph 19 again. The terms "therapeutic" and "sub-hepatotoxic" are not interchangeable.

Sub-hepatotoxic means nontoxic, right?

A. No, it does not.

Q. It's below the -- it's -- sub-hepatotoxic is below the level of toxicity.

A. No, no, no. We are not -- this statement cannot be reversed. That's kind of what you're doing. You're saying -- let me rephrase this.

The statement that a therapeutic dose is nontoxic is a truism, essentially. Of course a therapeutic dose is not toxic, right? That does not mean that all nontoxic doses are therapeutic.

Q. Your statement in the paragraph 19: Although it is tempting to refer to any sub-hepatotoxic dose or

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concentration of acetaminophen as therapeutic, that is incorrect.
You wrote that, right?
A. Yes, I did.
Q. And here you're writing: APAP toxicity shows a threshold dose-dependence such that therapeutic doses are generally considered nontoxic.
A. Yes. Once again --
Q. So you're saying that doesn't go in the reverse direction?
A. Absolutely not, no.
MR. COHEN: I think that was a double negative.
A. You're saying that doesn't go -- you're saying -- I'm sorry. Let me reconsider that. Maybe I made a mistake.
You're saying that -- you're saying that it doesn't go in the reverse direction. I'm sorry.
Yes, I'm saying that doesn't go in the reverse direction. I apologize. I'll try to slow down and consider it a bit more.
BY MR. JANUSH:
Q. So let me -- let me say this.

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Dr. McGill, I'm going to use this paper to make the point that nontoxic doses of acetaminophen that do not cause transaminase release and histological necrosis, i.e., doses that would be overdoses, can nonetheless lead to transient hepatocellular mitochondrial dysfunction and steatosis, right?
A. I don't know if that -- you're stating that that's what you're going to show.
Q. That's what you wrote, right?
A. I don't know if that's what you're going to show.
Q. You wrote that though. These are your words.
A. Sorry, you didn't tell me you were quoting anything in that question.
Q. I purposely didn't because I wanted to see if you were going to fuss with me like you have been all day. You just fussed with me over your own words.
MR. COHEN: Object to the form.
BY MR. JANUSH:
Q. So let's go to page 214.

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A. I'd like to state right away, what you said is not true. An overdose is really -- I mean, you can quarrel over what's a supertherapeutic dose, what's an overdose. An overdose is not just a dose that causes liver injury. An overdose is an excessive dose that's more than the therapeutic dose.
Q. Okay. Let's go to your conclusion, page 214. In conclusion, this study shows that even nontoxic doses of APAP that do not cause transaminase release and histological necrosis can nonetheless lead to transient hepatocellular mitochondrial dysfunction and steatosis.
Did I read that right?
A. Yes.
Q. Is oxidative stress associated with mitochondrial dysfunction?
A. In the case of acetaminophen overdose in the liver, oxidative stress is associated with mitochondrial dysfunction.
Q. Okay. And here, you're not addressing acetaminophen overdose. You're addressing a nontoxic dose that can nonetheless lead to mitochondrial

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dysfunction, aren't you?
A. No. This paper only looked at overdoses. The lowest dose we used was 75 milligrams per kilogram. A normal dose -- I'm sorry, may I please finish the question?
Q. I didn't interrupt you.
A. May I please finish the answer?
Q. I didn't interrupt you. I was silent.
A. So a normal dose in a human is one gram at one time. An average body weight for a person is 70 kilograms, although I'm not sure that applies to me. And so if you do that calculation, so that's 1,000 milligrams, right, one gram. Divided by 70 kilograms, you get about 14 milligrams per kilogram. That is far lower than 75 milligrams per kilogram.
Furthermore, the effects of transient mitochondrial dysfunction and steatosis were not observed at that lowest dose that we use, that lowest overdose, 75 milligram per kilogram.
And finally, the operative word here is "transient." The point of this

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paper, from my point of view as a scientist involved in this study, my interest in this was that at the time it was thought, by some people, anyway, that mitochondrial depolarization was an irreversible step in cell death, and that once that occurred, the cells would die. This paper demonstrated that that's not the case. So it was a transient effect from which the cells recovered quickly.

So again, these are still overdoses. Even the lowest overdose showed no effect, and even the effects that were observed at the higher dose was a transient effect and the cells recovered.

Q. So, first of all, just to be clear, we're talking about the liver again, right?

A. Yes.

Q. Okay.

A. Liver and overdose.

Q. And second of all -- I'm looking at your conclusion. Are we reading the same sentence: In conclusion, this study shows that even nontoxic, quote -- you quoted

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it, not me -- doses of APAP that do not cause transaminase release and histological necrosis can nonetheless lead to transient hepatocellular mitochondrial dysfunction and steatosis.

You said that, not me, right?

A. That's what we wrote in the paper. Nontoxic does not mean therapeutic.

Q. It also doesn't mean overdose.

MR. COHEN: Object to the form.

BY MR. JANUSH:

Q. Right?

A. Overdoses can be not overtly toxic.

Q. So is it your testimony in this case that you intended, when using nontoxic, no quotes, doses of APAP, to mean it's actually an overdose dose but it is not toxic?

MR. COHEN: Objection, form.

A. I mean, essentially, yes. It's -- it is still an overdose. It just didn't cause overt liver injury based on transaminase release and histology.

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BY MR. JANUSH:

Q. Here's where I'm stuck, and I'm going to have to ask you to help me get unstuck. Because after the exact sentence I read, you then use the words "Unlike overdose-induced hepatotoxicity, the effects of subtoxic APAP are comparably mild and reversible and correlate with JNK activation and mitochondrial translocation.

You wrote that, right?

A. That's what we collectively stated in the article.

Q. So you're addressing that this isn't -- this is unlike an overdose --

A. No, no. I said it's unlike overdose-induced hepatotoxicity.

Q. Right.

A. A critical point.

Q. Unlike overdose-induced hepatotoxicity. And then later you say: However, in patients subjected to other stresses, APAP-induced transient mitochondrial dysfunction may lead to overt transaminase release and necrosis.

What other stresses were you

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speaking about?

A. At that time, there had been some concerns about, for example, patients with chronic liver diseases taking acetaminophen may be more susceptible to acetaminophen toxicity. However, that idea is widely discredited now, partly through my own research.

Q. I'm going to move on to paragraph 20, where you address --

A. So paragraph 20 in my report?

Q. Paragraph 20 of your report at page 10, where you address that Dr. Cabrera and Dr. Louie try to justify the use of very large doses or concentrations of acetaminophen in experimental models by referencing human equivalent dose (HED) estimates from the U.S. Food and Drug Administration. And you say: This approach is scientifically invalid.

Did I read that right?

A. Yes.

Q. Are you actually saying that the reverse cannot be done, that you cannot have an AED, an animal equivalent dose?

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A. What I'm stating here is that the FDA guidance document -- I believe Dr. Louie tried to argue -- I can't recall if it was in his initial -- I believe -- actually, Dr. Cabrera and Dr. Louie have both tried to rely on this FDA guidance as stating that going in the reverse direction from humans back to animals is an acceptable approach. The FDA guidance document never says that.

Q. The reason the FDA guidance doesn't say that is because it was written in 2005 with a purpose to protect first-in-human-use scenarios, right?

A. That's correct.

Q. It --

A. Well --

Q. Are you aware of the fact that even today, the FDA is considering potentially doing a preclinical trial?

MR. COHEN: Object to form.

BY MR. JANUSH:

Q. A preclinical study.

MR. COHEN: Object to form.

A. I -- that's an incredibly broad

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question. I don't understand what you're asking me.

BY MR. JANUSH:

Q. So if the FDA wanted to test acetaminophen in utero, isn't the animal model the only way to ethically do that?

A. If they -- again, this is a very broad question.

Q. It's actually not a broad question.

A. No, no. For its --

Q. It's pretty narrow.

MR. COHEN: Let him finish.

A. Acetaminophen is currently an FDA-approved drug. There's no reason why you couldn't do a clinical trial in patients using therapeutic doses of acetaminophen in pregnant women.

BY MR. JANUSH:

Q. So -- so if, hypothetically -- and by the way, just to be clear, in your review, you also conclude just that, right? You say -- the last page, right --

MR. COHEN: Sorry, is this 839?

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BY MR. JANUSH:

Q. Back to 839. Right above the numeral 8: Even a simple study could be performed in which pregnant mice -- now you're talking about mice, not women -- receive 15 milligrams per kilograms APAP one to four times per day for several days, and behaviors associated with ASD and ADD/ADHD are measured in offspring over time.

Here you're saying you could -- there's no reason why you can't do an easy study with mice at low doses over time, right?

A. Yes, which does not preclude doing it in humans.

Q. You didn't address doing it in humans here, correct?

A. I didn't say that you can't do that in humans.

Q. I know. Now I'm going to ask you about the ethical implications.

If you are testing for something as serious as ADHD and -- and autism spectrum disorder in offspring, why would you use women, pregnant women and their

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offspring, as potential guinea pigs?

MR. COHEN: Object to the form.

BY MR. JANUSH:

Q. Wouldn't that be unethical?

A. Listen, I'm not an ethicist. I'm not a philosopher. I can't opine on that question.

Q. Do you know that your fellow experts for Johnson & Johnson say the exact opposite of you on this topic --

MR. COHEN: Object --

BY MR. JANUSH:

Q. -- and just testified on this topic stating that they would never permit a patient of theirs to be enrolled in a clinical trial where the endpoint is to determine fetal safety?

MR. COHEN: Object to the form.

A. What I stated is that because it's an FDA-approved drug, I personally am unaware of any particular reason why you couldn't look at -- for example, you could do an observational study in women who choose to take acetaminophen of their own volition.

So you're not administering it

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to them; they're choosing to take it. And you could just observe the outcomes, which is effectively what's been done in the epidemiological studies -- well, anyway, certain ones.

In addition to that, as I stated, I'm not an ethicist and I'm not going to comment on the ethics of any kind of study design.

BY MR. JANUSH:

Q. You understand, though, that the reason it's done retrospectively in epidemiological studies is specifically because you cannot test on pregnant women and their babies for injuries?

MR. COHEN: Object to form.

BY MR. JANUSH:

Q. Like what institutional review board would commit to passing this test?

MR. COHEN: Object to form.

A. Once again, I'm not an ethicist. I can't comment on the ethics of a trial like that. In addition, there are many reasons to do different kinds of studies. I'm sure there are more than one in the case

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of epidemiological studies.

BY MR. JANUSH:

Q. Okay. You know, I have to go back before I go forward with the document that I had given you a moment ago. I forgot to deal with something with you.

At paragraph 17, page 11 of your report, you address conversely all drugs --

A. Sorry, page 11 doesn't have paragraph 17, so I want to make sure I'm looking in the right spot.

Q. My apologies. I apologize. Page 8, Toxicology and Drug Safety.

A. Uh-huh.

Q. Paragraph 17 at the bottom of the page: Conversely, all drugs can be used safely at some dose.

A. Yes, this is a fundamental tenet of toxicology.

Q. Do you appreciate that what you just described as a fundamental tenet in toxicology is -- that there isn't necessarily a one size fits all, that all drugs can be used safely at some dose, meaning -- let me

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ask it differently.

Do you appreciate the concept that a safe dose of Tylenol for an adult mother may be unsafe for a developing fetal brain?

A. I'm aware of the concept of genetic susceptibility. I have not seen any data suggesting that what you've stated is correct.

Q. Okay.

A. Sorry, any reliable, rigorous, reproducible scientific data.

Q. I'm not even going to address data. I'm just going to address logic and FDA guidance.

As you sit here today, do you know whether infants, postnatal, should be given an adult dose of Tylenol?

MR. COHEN: Object to the colloquy that preceded the question.

Go ahead.

BY MR. JANUSH:

Q. Should infants be given an adult dose that's safe for an adult of Tylenol?

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A. So typically, when you dose, you don't just give -- well, first of all, I'm not a physician, certainly not a pediatrician. Can't really comment on what should or shouldn't be done.

I'll just leave it at that.

Q. Let me give you the dosing guide for Tylenol from Johnson & Johnson. We'll mark this as P836.

(Whereupon, Deposition Exhibit P836, Dosing for Tylenol Children's & Infants' Medicine, was marked for identification.)

BY MR. JANUSH:

Q. If you look at the Infants Oral Suspension, acetaminophen, 160 milligrams per 5 milliliters, weight less than 24 pounds, less than 2 years, ask a doctor.

But when you're not a baby and you're two to three years old and you're not in utero, you're limited, if you weigh between 24 and 35 pounds, to 160 milligrams as your dose per 4 hours.

160 milligrams per dose is by no means the adult dose for Tylenol, right?

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A. I haven't done the math for this. I couldn't say. And in any case --
Q. No math needed. It says 160 --
MR. COHEN: Wait, wait, wait. He hadn't finished. Go ahead.
A. Doses are typically expressed scientifically as milligrams per kilogram.
BY MR. JANUSH:
Q. It's 160 milligrams per 5 milliliters, you see that above, under Infants Oral Suspension?
A. Yes. What that means is you administer a volume of 5 milliliters that contains 160 milligrams.
Q. Right.
A. They also base this dosing on weight, right? Because scientifically, when you express a dose, it's milligrams per kilogram.
Q. But they're giving an infant 160 -- not an infant, a two- to three-year-old, a limitation of 160 milligrams, and no such similar limitation exists for an adult, right? An adult dose is different and larger, true?

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A. We mean different things when we say "dose." As a toxicologist or pharmacologist, dose is normalized to body weight. This 160 number is not normalized to body weight. In fact, my guess -- again, I'm -- I don't work for the FDA, I don't work for J&J. I'm not a physician.
My guess would be this is weight -- I mean, you have to, when the weight is different, you have to adjust the dose.
Q. Right.
A. So yes, this is not a surprise to me at all.
Q. This is similar to allometric scaling, right? You're scaling down from an adult to a 24- to 35-pound toddler that's two to three years old and giving a lesser dose than the adult dose.
MR. COHEN: Objection, form.
A. No, this is not an example of allometric scaling. Not in any form.
BY MR. JANUSH:
Q. I said similar.
A. I would not even characterize

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it as similar.
Q. Okay. So when you say conversely, all drugs can be used safely at some dose, do you appreciate that there is a distinction of what a safe dose might be for a mother versus -- who is pregnant versus what the safe dose might be for her in utero developing baby that weighs far less than 24 pounds?
A. Let me preface this again: I'm not a physician. I'm not a pediatrician. I'm not an obstetrician. I can't comment much beyond saying -- pointing out the fact that you are -- you seem -- well, I'm sorry, I don't want to judge what you're trying to say.
My understanding of what you're trying to say is that the dose that the mother takes, that's exactly what -- as long as the baby is in utero, that's what the baby sees. That's incorrect. The drug is distributed throughout the mother and the reproductive unit.
So -- and, in fact, arguably, you could say that it's a lower dose than

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what an adult would normally get.
Q. We're going to get there too. Promise you.
(Whereupon, Deposition Exhibit P811, A simple practice guide for dose conversion between animals and human, by Nair et al., was marked for identification.)
BY MR. JANUSH:
Q. I was talking about allometric scaling with you a moment ago. I'm going to hand you P811. It's: A simple practice guide for dose conversion between animals and human.
Have you ever seen this article, this journal that was -- this journal article published in the Journal of Basic and Clinical Pharmacy in 2016 --
A. Not --
Q. -- by Anroop Nair and Shery Jacob?
A. Not to my recollection.
Q. So if you turn to --
MR. COHEN: Can he have just 30 seconds to look at the document?

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MR. JANUSH: Yeah, sure.
MR. COHEN: Thank you.
(Document review.)
BY MR. JANUSH:
Q. And just to guide you with what I'm seeking to do here, I'm seeking to address the fact that there's a Table 1 with a human equivalent dose calculation and a Table 2 with an animal equivalent dose calculation or an AED.
And for the moment, I only seek to address the notion that these authors have addressed how you scale a human equivalent dose based on body surface area and conversely or similarly, an animal equivalent dose calculation, which also includes human within the species to convert from.
Do you see that?
A. I'm sorry, specifically what -- you're asking do I see the --
Q. Do you see Table 2, human -- at the top of Table 2 and human at the top of Table 1. In other words, when you scale an HED, obviously humans are involved. When you scale an AED, an animal equivalent dose,

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humans also can be involved in that conversion.
Do you see that?
A. I see the tables and I see the word "human" at the top lines.
BY MR. JANUSH:
Q. Incidentally, what's the most significant publication you've ever had that's been broadly accepted in the scientific community and cited in an incredible way, like high numbers? Do you know? Have you ever reviewed your literature to see how well you're cited?
A. Because I have to provide certain metrics like citations and h-index and so on for, you know, faculty reviews, that sort of -- or annual reviews, that sort of thing, I do occasionally look.
My highest cited original article is one that was published in 2012 in the Journal of Clinical Investigation, in which we demonstrated for the first time, using samples from humans -- acetaminophen overdose patients -- that mitochondrial damage also occurs in humans after

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acetaminophen overdose in the liver, similar to the way it does in mice. That had been known for a long time. No one had shown it in mice previously.
I'm sorry, that had been known for a long time in mice. No one had shown it in humans previously.
Q. How many citations?
A. Off the top of my head, I don't recall. Maybe 300 to 500, somewhere --
Q. Yeah, that's what I saw when I looked at your highest work as well. And some of your other work, I saw less than a hundred for some, a hundred, 200 for one of them. Wouldn't surprise you of the numbers I'm saying, right?
MR. COHEN: I'm sorry. Is this a question?
BY MR. JANUSH:
Q. In other words, range of between less than a hundred and 300 for citations of your literature is something you'd expect, right?
MR. COHEN: Object to form.
A. I have a number -- I mean, I

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have many publications published over -- that have been available over different lengths of time and have accumulated different numbers of citations. You know, some of them are hundreds and hundreds and some haven't been cited yet.
BY MR. JANUSH:
Q. Okay. Want to take a guess how many times this Nair article has been cited, the simple practice guide for dose conversion between animals and humans?
MR. COHEN: Object to form.
BY MR. JANUSH:
Q. Let me help you because I'm sure you don't want to guess. 812B.
(Whereupon, Deposition Exhibit P812B, ReadCube Citation Reference, Nair article, was marked for identification.)
BY MR. JANUSH:
Q. 3,127 citations, according to ReadCube, but when you go on Google Scholar, 3800 citations. That's a lot of citations for a concept that is nonsensical and not widely adopted, right?

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MR. COHEN: Object to form.
Is that a question?
MR. JANUSH: It sure is.
A. I'm happy to address this. First of all, the most widely accepted source for citation numbers is Web of Science. That's because --
BY MR. JANUSH:
Q. I'll give you my laptop. You want to do it with me?
A. Please allow me to finish the question. We can do that if you like, but I have additional answers -- or additional parts to the answer.
So it's well known that other citation databases, especially Google Scholar, overcount citations.
In addition to that, a couple of other things. What you don't have in this information is whether or not those citations are positive or negative. For all I know, every single citation could be saying what these people say, don't do that, right? We have no way of knowing if the people citing them are affirming it in this room or

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rejecting it.
Q. Actually, we do. Because there's also a --
MR. COHEN: Were you done with your answer?
THE WITNESS: No, I was not.
MR. COHEN: So let him finish, please.
A. Just give me a moment. I've lost my train of thought a bit here.
Oh, in addition to that, as a scientist, it's not my practice and it's not common practice to judge the value of a publication based on citations, journal, authors, institutions. We judge it based on the content.
I have no idea -- well, and the simple fact of the matter is I strongly disagree with this content, and the plaintiffs' experts cite the FDA guidance to endorse this kind of concept, but the FDA guidance absolutely does not endorse it. It says nothing about animal equivalent dosing.
BY MR. JANUSH:
Q. And again, you appreciate that

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the FDA exists to protect human beings, right?
MR. COHEN: Object to the form.
BY MR. JANUSH:
Q. It doesn't exist to protect mice, right?
MR. COHEN: Object to the form.
A. So I agree with your earlier statement and, in fact, that the FDA guidance document says this itself, that the purpose of human equivalent dosing is to protect the first-in-human subjects -- I'm not quite done with my answer.
BY MR. JANUSH:
Q. I didn't interrupt you. I'm just shaking my fingers.
MR. COHEN: You are.
MR. JANUSH: I'm not interrupting.
MR. COHEN: So please don't shake your fingers at the witness.
THE WITNESS: I take that as a sign --
MR. JANUSH: No, no. Meaning like I want to talk in a moment. Go

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ahead.
THE WITNESS: I apologize, I interpreted that as a sign that you wanted to speak. My mistake. Sorry, let me --
A. So my question, then, is -- there's a clear purpose for using that approach to go from animal studies to humans. What is the clear purpose from going from human doses to animals using this approach?
BY MR. JANUSH:
Q. The clear purpose is that babies' lives are at stake. Do you understand that in this case?
MR. COHEN: Object to the form.
BY MR. JANUSH:
Q. Babies' lives, their brains are at stake. So you test by looking at human doses and you apply that to animals so that you can get the best test you can, because there is something called a post-manufacturing and sale need for safety, isn't there, Doctor?
MR. COHEN: Object to the form.
A. I disagree with what you seem

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to be defining as a human dose. You seem to be wholesale accepting that this animal equivalent dosing is the way to go and that these reflect human doses.

There's an enormous problem with that in the case of acetaminophen. We know very well the pharmacokinetics, the blood concentrations, the duration of exposure that humans are exposed to at therapeutic doses of acetaminophen. There's no need to do this. We can just give different doses to mice and look at the plasma concentrations.

Effectively, this has absolutely no applications to acetaminophen. Whether you agree with this approach or not in general, it is irrelevant for acetaminophen.

BY MR. JANUSH:

Q. Only acetaminophen or irrelevant in general? This human equivalent dose, this going back -- backwards to animals.

A. Sorry. I -- just point of clarity because you said human equivalent

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dose. I'm referring to this idea of animal equivalent dosing.

Q. I mean, they're the same concept, just addressed slightly different --

A. No.

Q. -- within the table, right?

A. No, they're absolutely not the same concept. They use the same numbers to go back and forth, but again, the rationale for doing this to determine a human equivalent dose is clear. It's to protect first-in-human volunteers for these drugs.

Going backwards from human doses to animals using similar numbers is totally unnecessary in cases when you have a well-characterized drug where you understand exposure, you understand plasma concentration, you understand the pharmacokinetics. That's the case with acetaminophen. This has no relevance to acetaminophen. It's unnecessary.

Q. So what's an unsafe dose for a fetus based on all the knowledge you have as an acetaminophen expert?

A. Yeah, I'm not a clinician. I'm

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not a pediatrician. I'm not an obstetrician. I cannot --

Q. You said the numbers are well known.

MR. COHEN: Wait, were you finished?

A. What I said is that, again, we're talking about maternal ingestion of therapeutic doses. We know very well the numbers with regard to duration of exposure, concentration and so on in women, including pregnant women, from some studies what concentrations to expect.

What we're discussing here is about going back to animals, and what I'm saying is that this is totally unnecessary and not scientifically valid to go back to animal doses in the case of acetaminophen.

BY MR. JANUSH:

Q. At paragraph 22 of your report, moving back to your report, you wrote that: The toxicity of a drug is often organ specific. For example, the fact that acetaminophen overdose can cause injury to the liver does not mean that it also injures

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the brain. A liver is not a brain, and the brain does not play a major role in acetaminophen metabolism.

Do you disagree with the notion that APAP overdose is often associated with neurological damage too?

A. As I stated before, I'm not an epidemiologist. I cannot comment on the epidemiological associations.

Q. No, that's actually not an epidemiological association. I'm talking about specific causation.

Do you disagree that APAP overdose is associated with neurological damage?

MR. COHEN: Object to the form.

A. Look, this is not what I'm here to comment on. I was asked to address the questions that I've laid out in paragraph 4 of my expert report.

BY MR. JANUSH:

Q. If a scientist was to opine that there's no neurological sequelae from acetaminophen overdose, that would be misleading, wouldn't it?

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A. Again, I'm not here to address neurodevelopmental or neurobehavioral effects.
Q. Do you agree that acetaminophen increases both neuronal cytochrome P450 isoforms and CYP2E1 enzymatic activity and protein levels?
A. Absolutely not. At therapeutic doses, absolutely not.
Q. Are you aware of in vivo experiments which show that intraperitoneal administration of acetaminophen at 250- and at 500-milligram per kilogram injection induces neuronal death in the rat cortex?
A. I'm aware of the Posadas study that Louie referenced and that I believe you are referring to.
Q. And do you think it was just done wrong?
A. Yes.
Q. The study was flawed?
A. I would like to note that that study was not designed to address any sort of neurodevelopmental outcome. They were interested in this idea that acetaminophen

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may contribute to hepatic encephalopathy in overdose patients. That's what they were investigating.
For the purposes of their investigation, aside from the fact that they used rats and, you know, which are not a good species, generally speaking, for the study of acetaminophen toxicity, I wouldn't characterize it as a -- as a bad study for that purpose. For the purpose that we're addressing, it's a deeply flawed study.
Q. When you say rats are not a good species for acetaminophen testing, you say that because rats have a very high threshold to ward off hepatotoxicity, right?
A. No, I say it for multiple reasons. First of all, acetaminophen metabolism in rats is not quite the same as in humans or mice. They do more sulfation than glucuronidation.
In addition to that, the doses that you have to give to -- kind of what you're alluding to, the doses that you have to give to rats to achieve hepatotoxicity are far greater than what a human or mouse

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requires to achieve hepatotoxicity.
In addition to that, what your plaintiffs' experts have basically overlooked or ignored is everything that occurs downstream of NAPQI formation, with the possible exception of some mentions of oxidative stress here and there.
A lot of other things happen, right? We have mitochondrial damage. That leads to oxidative stress. The oxidative stress activates c-Jun N-terminal kinase by causing it to dis -- causing ASK1 to disassociate from thioredoxin.
I'm sorry, I'm going to fast. Let me slow down. So I'll restart.
So after an overdose of acetaminophen, you have NAPQI formation, right, in the liver. That binds to mitochondrial proteins. That leads to mitochondrial dysfunction. Mitochondrial dysfunction results in oxidative stress. The oxidative stress leads to dissociation of kinase -- an enzyme, protein for simplicity -- called ASK1, from another protein called thioredoxin that normally

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sequesters it and holds it inactive.
When it dissociates, the ASK1, through intermediary steps involving other kinases, other proteins of the same type, activates a kinase called the c-Jun N-terminal kinase, or JNK for short.
JNK then translocates to mitochondria, where it binds to a protein called Sab. Sab basically causes a change in another protein called SHP, S-H-P. SHP then dissociates -- or I'm sorry, let me rephrase that. SHP then inhibits S-r-c or Src.
Q. I think we're going to stop you and call the judge. I think I've had it.
Do you remember what my question was?
MR. COHEN: Object to the form.
MR. JANUSH: Yeah, my question was --
MR. COHEN: Hold on. Hold on.
MR. JANUSH: -- about rats.
MR. COHEN: You interrupted him. Let's just get that on the record.
MR. JANUSH: I have had enough,

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man.
MR. COHEN: Let's just get it out on the record.
BY MR. JANUSH:
Q. I don't want to hear your soliloquies about all science. I want to hear answers to my questions. I asked you about rats being less hepatotoxic. That's the whole question.
A. May I --
MR. COHEN: Hold on. Hold on. Here's how it's going to work today. You ask questions. You hear the answer. You may not like it. You don't interrupt him. Ask your next question. Keep going. You've got plenty of time.
THE WITNESS: I'd like to continue my answer, if -- is that okay?
MR. COHEN: Yeah.
MR. JANUSH: No, because I'm just going to move to strike, and it's going to get stricken, so it's wasting your breath and my time.

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MR. COHEN: Well, you asked a question that he -- he's obligated to give a complete and full answer to your questions, just as your experts did. And he's going to do that.
Now, if you don't want to do that and want to end the deposition, that's your choice.
THE WITNESS: I'm --
MR. JANUSH: If you would like to continue to filibuster, you do that. I will write my letter to the Court if I need to.
MR. COHEN: That is an inappropriate comment, just as many of the other comments you've made today. Please be a little more professional.
THE WITNESS: I'm getting to the answer to your question.
A. So you asked -- my understanding of your question is that -- is why do we think rats are a poor model for acetaminophen toxicity, right?
I'm telling you the mechanisms that we know occur in humans and in mice.

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The mechanisms in humans and mice so far appear to be identical from all the available data, and I'm trying to explain what's different in rats, okay?
So essentially, much of these downstream effects -- here we're just talking about, for the most part, plaintiffs' experts and myself have just addressed the NAPQI formation, a little bit about oxidative stress.
What I'm trying to convey is that there are many other events in the mechanism of toxicity, and some of those additional events in rats do not resemble what we know to occur in humans and mice.
That's why, for those three reasons, the resistance to hepatotoxicity requiring higher doses, differences in metabolism and differences in mechanistic -- other mechanistic endpoints, that's why we don't consider rats a good model for human acetaminophen hepatotoxicity.
BY MR. JANUSH:
Q. Okay. When you're speaking in front of an audience, you've acknowledged

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that rats are not a good model because they are so resistant to acetaminophen toxicity, right? It's just a yes or no.
When you've spoken in front of people as a panelist, that's what you've acknowledged in simple terms in one straight sentence, right?
MR. COHEN: I'm sorry, object to the form. This is improper deposition conduct. You can't tell a witness, say yes or no. Just ask your question.
MR. JANUSH: I can --
MR. COHEN: He'll give you his answer. And then if you don't like it, you can ask another question, you can move to strike, but please, don't lecture him all day on how he should be answering questions. It's inappropriate conduct, Counsel.
BY MR. JANUSH:
Q. Sir, can you answer my question?
A. Your question is -- I just want to make sure I understand.

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Q. When you've been a panelist, in plain, unspoken, simple terms, you've set forth in one sentence why rats are not a good model for testing on acetaminophen, right?

A. I don't recall every single public speaking engagement I've had or what I said in every single one. However, making that one statement, first of all, it doesn't preclude other reasons, and second of all, when you're speaking in front of people, there's usually a time limit or some sort of expectation for time, and I'm not necessarily going to go into a long monologue on every possible reason. It's usually sufficient for those purposes to just give one or two and move on.

Q. Okay. We're going to play a video clip. We're going to mark this as Exhibit 870.

(Whereupon, Deposition Exhibit P870, Media File, Measuring Toxicity Biomarkers, was marked for identification.)

(Whereupon, Exhibit 870 was played aloud in the deposition room.)

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BY MR. JANUSH:

Q. So I just want to ask: Was that you that we just heard speaking?

A. It sounds like me and I recall this webinar.

Q. Okay. Thank you.

MR. COHEN: When it's convenient, let us know if you want to -- when you want to take a break. It's over an hour.

MR. JANUSH: I don't want to, but if you'd like to, I will accommodate, absolutely.

MR. COHEN: When you get to a breaking point.

MR. JANUSH: Okay.

BY MR. JANUSH:

Q. By the way, going back to Posadas. Posadas 2010 was testing rats at 250 and 500 milligrams per kilogram, far less than the toxic doses that you just -- that we just played from your presentation, right?

A. Again, a sub-hepatotoxic dose, the term is not interchangeable with therapeutic dose. That's very clear in the

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Posadas paper, in fact, because you can look at the plasma concentrations that those doses resulted in, and they are 1 millimole per liter to two millimoles per liter.

Just for reference, the maximum therapeutic concentration that you typically achieve at a -- with a dose of Extra Strength Tylenol is around 132 micromoles per liter. So 1 to 2 millimole per liter is 1,000 to 2,000 micromoles per liter. That absolutely cannot be said to mimic human exposure to acetaminophen at therapeutic doses.

Those are extremely high concentrations. Those are the concentrations you see in a human at overdose.

Q. Actually, I'm thinking that the math is done wrong here because Posadas found that acetaminophen can cause concentration-dependent neuronal death in vitro at concentrations, as you said, of 1 and 2 millimolar per millimeter [sic], but that's well below the stated concentrations observed in humans, which ranges from 66 to 198 micromolars, right?

MR. COHEN: Object. We don't

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have Posadas marked.

MR. JANUSH: Don't need to. I'm just talking about the math here.

MR. COHEN: No, you're talking about Posadas.

THE WITNESS: Yeah, I don't know what you're reading from.

BY MR. JANUSH:

Q. These are my notes, not Posadas.

A. May I hear the question again?

Q. Sure.

MR. COHEN: Are you relying on Posadas? Because if you are, maybe you can hand it to him and you can simplify this.

MR. JANUSH: You can say objection, form only and not coach. I don't need to hand a document over when I want to question about a topic. I don't need to.

MR. COHEN: That's inappropriate conduct.

A. If we're asking a question --

MR. JANUSH: It's not

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inappropriate. You just coached your witness to ask for a document.

MR. COHEN: That's nonsense.

MR. JANUSH: That is absolutely what you did. The depo protocol is "objection, form." If he needs to see something, he's a real bright guy, he can ask me for it.

BY MR. JANUSH:

Q. Witness, let's go back, Dr. McGill to my question: Posadas -- do you know whether Posadas 2010 found that acetaminophen can cause concentration-dependent neuronal death in vitro at concentrations 1 and 2 millimolars per milliliter?

MR. COHEN: Objection, form.

A. I would like to see the paper since you are asking me specific questions about it. I don't recall off the top of my head at what dose they claim to have observed neuronal toxicity.

The doses that they administered to rats, which is what they used to guide their in vitro dosing per my

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recollection of the paper, that resulted in plasma concentrations of 1 to 2 millimole per liter, which is the same as 1,000 to 2,000 micromoles per liter, which is much higher than the human therapeutic exposure -- maximum human therapeutic exposure of around 130 micromoles per liter.

BY MR. JANUSH:

Q. What literature can you point to that concludes, if you solely look at how acetaminophen poses hepatic effects, you can extrapolate what the effect of acetaminophen will be on the human brain?

A. That is a very broad question. I mean...

Q. Looking at your report, what have you cited to in your expert report that helps you conclude that if you look at how acetaminophen poses hepatic effects, you can extrapolate what the effect of acetaminophen will be on the human brain?

A. Your expert -- I'm sorry, I don't mean to say "your."

Q. Not my expert. We're talking about you. What can -- did you point to in

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your report --

MR. COHEN: I'm sorry.

MR. JANUSH: No, no. This is unfair now.

MR. COHEN: You just interrupted him.

MR. JANUSH: He can't talk about my expert when asked about what is in his report.

MR. COHEN: I'm sorry, you cannot interrupt the witness. Just let him answer and ask the next question.

A. My -- my report is, in part at least, a response to the plaintiffs' experts, so I think it's reasonable, necessary in this case, to reference the plaintiffs' experts' opinions or speculation, really.

So the plaintiffs' experts have speculated on a few possible mechanisms. That's what I was asked to address.

So when I look at the data with respect to those possible mechanisms, the speculative mechanisms by which the plaintiffs' experts opine acetaminophen might

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cause toxicity in the brain, we just see no evidence to support it.

There's -- as I've laid out in my report, there's very, very little CYP2E1 in the brain relative to the liver. Those studies in which they have looked at, you know, acetaminophen-protein adducts in the brain have found none, and yeah, there's just -- so I was asked to address those issues. That's what I've done in my report. I find that the data don't support the claims of the plaintiffs' experts.

MR. COHEN: Is this a convenient moment to break?

MR. JANUSH: It sure is. Whenever you would like.

MR. COHEN: Thank you.

THE VIDEOGRAPHER: We are going off record. The time is 1:37.

(Recess taken, 1:37 p.m. to 1:54 p.m. CDT)

THE VIDEOGRAPHER: We're going back on record. The time is 1:54.

BY MR. JANUSH:

Q. Dr. McGill, I'm going to have

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you turn to your report at page 18, the second paragraph of -- or second portion of paragraph 29. Let me know when you're there.

A. I'm there.

Q. Okay. I'm reading from the second line down: Glutathione is available in sufficient amounts in the liver to detoxify NAPQI after human therapeutic doses of acetaminophen.

Do you see that?

A. Yes.

Q. Is that statement true, in your opinion, for in utero fetuses exposed to an adult dose of acetaminophen in the second trimester?

A. So in my expert report, I reference -- or it briefly describes a number of studies that measured glutathione in the human brain, including a couple that looked at the fetus. I -- off the top of my head I don't recall exactly what trimester, but they did show that there was millimole per liter quantities of glutathione in the fetal brain just like the adult brain.

Q. So do you believe that in utero

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fetuses exposed to an adult dose of acetaminophen in the third semester has sufficient glutathione available in the liver to detoxify NAPQI after human therapeutic doses of acetaminophen?

A. So now you're asking third trimester in the liver?

Q. I am.

A. So I'm trying to recall studies that I cited with respect to glutathione measurement in -- in vivo that may -- that involved fetal measurement.

(Document review.)

A. So in at least one of the studies that I cited in my report, they were able to detect glutathione levels in the liver of the fetus, so it is present. I would expect it to be present, again, at millimolar concentration.

Q. Was there -- what study was that that you're relying to, that one study?

A. That particular one that I was looking at --

Q. Yeah.

A. -- at that moment -- I'm sorry,

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I have to find it again.

Q. And what page are you on?

A. Ah. So this is the Raijmakers. It's page 41.

Q. Uh-huh.

A. And I haven't looked through all of these, so I'm not sure if --

Q. Let me just ask something on Raijmakers since you cited it as a relevant study.

Zero acetaminophen tested in Raijmakers, right? Absolutely none, right?

A. To my recollection, they weren't looking at acetaminophen, right. They were looking at glutathione levels.

Q. So it -- it's -- it can't be a relevant study in response to my question if my question was, quote: Is that statement true in your opinion for in utero fetuses exposed to an adult dose of acetaminophen in the third trimester?

A. Well, I disagree with your statement it can't be relevant. What they've demonstrated is that there is glutathione in the liver, in the fetus. Generally speaking,

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glutathione is present at millimole per liter concentrations in the liver and throughout the body. Millimole per liter concentrations are high biologically. It's quite high.

So if there's glutathione present, then I would absolutely expect it to detoxify NAPQI.

Q. And for that opinion, you would look to Raijmakers et al. on page 41?

A. A number of studies. So every study that I'm aware of that has measured glutathione in tissues throughout the body, whether we're talking about brain, liver, any other tissue, including this study, has found, although -- well, has found high millimole per liter concentrations.

So I'm relying on -- this is one study that I've specifically pointed out as an example in response to your question, but there are numerous studies that support what I just said.

Q. And if we move forward to Acetaminophen Pharmacokinetics During Pregnancy at page 20, this is a section where you're addressing: Published studies

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reporting differences in acetaminophen metabolism and pharmacokinetics between pregnant and nonpregnant women that are unlikely to have significant clinical impact. No published study provides direct data on embryonic/fetal acetaminophen metabolism in humans. Major studies reporting data on acetaminophen in pregnancy are described below.

Right? That's what you're addressing in this section?

A. Well, you've read what I've written.

Q. Okay. So let's go to paragraph 32 where you address that: Acetaminophen must traverse the blood-placenta barrier to reach the embryo or fetus.

And you write: Acetaminophen has been shown to cross the placenta after maternal use.

And I'm going to skip the next sentence and address: However, acetaminophen concentrations in umbilical cord blood after maternal ingestion of therapeutic doses have

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been reported to be nearly identical to the low concentrations in maternal blood, prompting the conclusion that maternal use of acetaminophen at the currently recommended dose is unlikely to lead to accumulation of potentially toxic levels in the fetus.

Did I read that correctly?

A. Yes.

Q. Okay. And after making that last statement, you cite to a single case reported at footnote 50. It's the Nitsche study, right?

A. That is what's listed for the footnote.

Q. Okay. And this concerned a neonate to address -- and you used this study to address that maternal use of acetaminophen at the currently recommended dose is unlikely to lead to accumulation of potentially toxic levels in the fetus. Right?

A. That's a quote from that study. It's not my words.

Q. Right. I understand that.

Dr. McGill, I'm going to provide you with -- where is 813? I'm going

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to provide you with 813.

(Whereupon, Deposition Exhibit P813, Transplacental Passage of Acetaminophen in Term Pregnancy, by Nitsche et al., was marked for identification.)

BY MR. JANUSH:

Q. This is the Nitsche study. It's Transplacental Passage of Acetaminophen in Term Pregnancy. It's published November 2016 online, and let me ask you something.

What was the goal of the Nitsche-cited -- Nitsche study you cited, or stated differently -- let me help on this.

This was the study, was it not, where pregnant women undergoing scheduled cesarean section deliveries were given a dose of 1,000 milligrams of acetaminophen just before they gave birth, and the acetaminophen levels were then tested in the mother and neonate as soon as 30 minutes after the maternal administration of the drug, right?

A. If you don't mind, I'd like a little bit of time to refresh myself.

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Q. Sure. And just to give you guidance on where I was addressing that from, it was the second page, center of the left side, starting with "Acetaminophen is widely used in pregnancy."

But really, I'm addressing the language: This report suggests that the level attained in the neonate after a single maternal dose of acetaminophen is similar to the levels obtained after an oral dose administered directly to the neonate.

And then if you look at the study design just below, you'll see the 1,000 milligrams, single oral dose upon admission for scheduled cesarean section -- cesarean section.

Do you see that, a few sentences down from the word "study design" in big bold letters? And it's also on the screen to guide you in front of you, to prompt you. You should definitely allow the screen to help you. It will help.

(Document review.)

BY MR. JANUSH:

Q. And if we turn to the third

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page, and it's the final page. It's a real short study. At the Conclusion: Maternal and fetal acetaminophen levels are comparable as early as 30 minutes after administration, indicating rapid placental transfer of the drug.

Notably, acetaminophen PKs in fetal samples closely parallels behavior of the drug in the maternal system. The time to peak concentration and half-life are similar, and the fetal AUC is nearly the same as the maternal AUC.

Do you see that?

A. I see the statements.

Q. Okay.

A. I'd like to note, these are technically not fetal samples, right? They're neonates who were delivered by cesarean section, so we're talking about exposure very late in pregnancy at the time of delivery.

Q. Right.

A. This is not fetal development, it's not embryonic development.

Q. Right. Yeah. And you cited to

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this, not me, right?

A. Yes, I cited to it.

Q. Okay. So -- and you cited to it as relevant to your expert report in a case involving fetal neurodevelopmental issues, right?

A. I cited to it as relevant data showing that there's transplacental passage of acetaminophen.

Q. Okay.

A. But again, I didn't say that these should -- I didn't say that this study, in my report, does or does not comment on the embryonic or fetal development. It does not. This is neonatal.

Q. Understood.

A. But I didn't state that in the report.

Q. But you did say -- you did say "prompting the conclusion that maternal use of acetaminophen at the currently recommended dose is unlikely to lead to accumulation of potentially toxic levels in the fetus."

You did say that, right?

A. I was quoting the authors of

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this study. It's a direct quote from the study.

Q. I understand.

But when you take a quote from the study and include it as a concluding sentence in a paragraph, you are adopting their conclusion in your report, right?

You're not saying anywhere here "and I disagree with this conclusion," are you?

A. My statement was that the data prompted the authors to conclude, and then I directly quoted them.

Q. Right.

A. I was saying that it prompted them to conclude it. I wasn't saying it was my conclusion.

Q. Okay.

A. I think it's a reasonable conclusion.

Q. You do?

A. From the data in that study.

Q. Okay. So --

A. And from the other data that I've seen.

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Q. So help me on this, because would you agree with the notion that prompting the conclusion that this recommended dose is unlikely to lead to accumulation of potentially toxic levels in the fetus, that conclusion is addressing a safety issue, right, toxic levels in the fetus?

MR. COHEN: Object --

BY MR. JANUSH:

Q. Fair to say?

MR. COHEN: Object to the form.

A. I can't comment on what the authors intended to convey with that statement.

BY MR. JANUSH:

Q. Okay. Well, let's comment on what you can address.

Can you point to any studied endpoints in this three-page piece of literature that addresses where the authors were studying safety to the fetus? Anywhere?

MR. COHEN: Object to the form.

BY MR. JANUSH:

Q. I mean, I -- the reason I'm

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asking is I only see discussion concerning the levels of acetaminophen observed just after cesarean section. So I'd like to know how the authors could have arrived at a safety conclusion in the absence of endpoints on safety.

MR. COHEN: Object to the form.

Go ahead.

A. I can't comment on the authors' thought process. My understanding of what they're trying to say is that the -- from the data available in this manuscript, the pharmacokinetics, or at least plasma concentrations of acetaminophen, appear to be similar in the mother and the neonate at the time of delivery. And I suppose they're making the assumption that you can extrapolate that to earlier fetal development.

BY MR. JANUSH:

Q. Well --

A. And we know that those therapeutic blood concentrations in the mother are deemed safe. Those are the -- that's a -- the 1-gram dose is what is

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recommended by the manufacturer and what the FDA allows, so it's considered a safe dose, and they get the same blood concentration.

So I think that's the reasoning of the authors, but again, it's the authors' reasoning.

BY MR. JANUSH:

Q. Yes, I get you. You quoted this, though, to address that the authors concluded that maternal use of acetaminophen at the currently recommended dose is unlikely to lead to accumulation of potentially toxic levels in the fetus, and I'm just asking you to point me to where toxicity was studied, if at all.

It wasn't here, right? I mean, it's a simple issue. I'm just asking you if you agree that it wasn't studied here.

MR. COHEN: Objection, form.

A. I think you have to take it in the context of the greater literature, right? The greater literature, as I've described in my report, shows that there is little to no CYP2E1 in the brain, so there's no -- also -- the literature also show there's no

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acetaminophen-protein binding in the brain, indicating no NAPQI formation in the brain.

The literature also show that there is no -- or that there is glutathione present in the -- in the brain, including the fetal brain, and so -- and databases show that also the low levels -- little to no CYP2E1 present in the brain extends to human -- different stages of human fetal development.

So when you put that all together with the fact that there's extremely low to no potential for NAPQI formation in the brain, even if it did form, there's glutathione to scavenge it. And we know that that works really well with these concentrations of acetaminophen in adults. There's no reason to think it wouldn't also work very well at these concentrations in the -- in the child.

BY MR. JANUSH:

Q. You just assumed a lot as to what the authors were concluding, didn't you?

MR. COHEN: Object to form.

A. I was giving my opinion that

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the data have to be interpreted within the greater context of the literature. I can't say the authors did that or not. Within the greater context of the literature, their conclusion was reasonable, however.

BY MR. JANUSH:

Q. Well, let's talk about what the authors actually said, because they said something vastly different from what you said.

Last paragraph: Although the current study suggests that fetal exposure to acetaminophen can be predicted using maternal drug levels, further study of acetaminophen metabolism to NAPQI in the fetus is clearly needed to better understand the risk of fetal harm after maternal acetaminophen use.

You see that?

A. I see their statement.

Q. It's very different from what you just said, right, about the body of literature that you take into consideration to conclude safety?

A. Well, again, I can't say what the authors were thinking or what the

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rationale was at the time.
Q. You can. It's in black and white, right, on this page?
A. No, no. They haven't said how they arrived at their conclusion based on these data, other than we know these levels are safe in adults, probably safe in the fetus too; or rather, the levels in the neonates was not higher than what you see in adults. So that's part of their reasoning. I can't comment on the rest of their reasoning.
Q. Do these authors demonstrate that the neonate is able to maintain high doses, high levels of -- to counter repeated exposures, high levels of NAPQI?
A. I'm sorry, you --
Q. I mean of -- yes, that is what I mean.
A. I don't think the question makes sense.
Q. I mean glutathione. I meant to say glutathione. Sorry.
MR. COHEN: Can you repeat the question?

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MR. JANUSH: I apologize.
BY MR. JANUSH:
Q. I meant to simply say: Do you believe that there's sufficient levels of glutathione in a neonate to endure repeated exposures at this level in utero with no downstream neurotoxic effects?
A. Well, again, I can't comment on these neurodevelopmental outcomes. Do I -- if the question is do I believe there's glutathione -- sorry, were you asking in the brain or the liver?
Q. Brain of the baby.
A. In the brain of the baby. Well, in fact, we know there's glutathione in the brain of the baby. I mentioned that Raijmakers study, right.
Q. Uh-huh.
A. So -- and in fact, in that study, they actually noted that the concentration in the brain was higher than the concentration in the fetal liver. So there's clearly glutathione present.
We also know from, for example, the Allen Institute for Brain Sciences

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database, their LMD microarray database, and from one of the studies I cited in my report, one of the publications, that fetal expression of P450s in the brain is still very low compared to the liver.
So given that information, there's glutathione present, there's very little P450. We have not only no reason to believe that they would have toxic effects; we have strong reason to doubt that there would be toxic effects in the fetus in the brain.
Q. So I'm going to circle back to Raijmakers in a moment. I want to go to the last sentence of this paragraph: However, our findings suggest that maternal use of acetaminophen at the currently recommended dose is unlikely to lead to accumulation of potentially toxic levels in the fetus.
Do you see that?
A. I see the statement.
Q. What are their findings that they're pointing to in this literature?
A. Again, I can't comment on --
Q. I mean, you used the

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literature, so I'm -- do you read literature constructively when you cite it in an expert report?
MR. COHEN: Object to form.
A. I cannot comment on the rationale of the authors at that time.
BY MR. JANUSH:
Q. Did you read literature constructively to determine, gee, did the authors get this right? Did they have actual data to support their conclusion?
Do you do that?
MR. COHEN: Objection, form.
A. Their data are consistent with my -- with the information in my report. I cannot comment on what they were thinking at the time.
BY MR. JANUSH:
Q. I'm not talking about their data about the acetaminophen passing from the mother to the baby in doses that mirror the mother. That -- that is not what I'm talking about.
I'm talking about their data regarding a safety point. Where is the

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safety data in this three-page study? Can you point me to it?

Because the way I'm reading this, I see a conclusion about our findings, quote. And I don't see findings about safety. So I'm trying to find whether this was a gratuitous statement and that -- or not. And I'd like your guidance on that.

A. I can tell you how I would interpret this in the context of the greater literature -- as I mentioned, how I interpret it in the context of the greater literature as evidence for safety. I can't comment on what they were thinking at the time.

Q. But you do see that they wrote our findings. In other words, they weren't looking at the body of literature. They were looking at our findings.

A. Okay. So one issue with that is they may have other findings than what's in this report, right. I can't say off the top of my head.

Q. How do you feel comfortable citing to this piece of literature --

MR. COHEN: Object to the form.

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BY MR. JANUSH:

Q. -- for safety -- to include the safety conclusion at footnote 32, when there's no safety endpoints addressed in the literature?

A. Yeah, as I explained, all the literature that I've -- as I've described in my report, all the literature show there is little to no CYP2E1 in the brain, there is no NAPQI formation or presence in the brain. There is glutathione in the brain that is available to scavenge NAPQI if any did form.

And so when you take that with the fact that the concentrations to which the fetus -- well, in this case, again, this is neonates. It's not really fetus, but fine -- to which the fetus was exposed is similar to what we're exposed to, then there's simply no reason -- taken as a bigger picture, it's strong evidence for the safety of -- for the safety of the fetus with this exposure to acetaminophen, with maternal ingestion of therapeutic doses of acetaminophen.

Q. You mentioned the Raijmakers study. Wasn't that of only two fetuses?

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A. I don't recall off the top of my head. You'd have to show me the report.

Q. I mean, you were referencing it from your report as something supportive of your opinions, so I'm just drilling down.

A. I'm happy to comment on it if you can produce a copy of the paper.

Q. I can't. Raijmakers -- do you remember if Raijmakers completely failed to look at any regenerative capabilities of glutathione?

MR. COHEN: Object -- object to the form.

A. Again, if you produce a copy of the paper, I'll be happy to comment on it.

BY MR. JANUSH:

Q. In Raijmakers, do you remember that there was absolutely no indication whatsoever as to whether acetaminophen had been used before there was testing done?

MR. COHEN: Object to the form.

A. Again, if you produce a copy of the paper, I'm happy to comment on it.

BY MR. JANUSH:

Q. It's something you cited, sir,

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so I'm just coming back to you on whether you know your own literature that you cited.

MR. COHEN: Object to the form.

A. I cited it because it shows that there is glutathione present in the fetal brain and as well as the fetal liver.

BY MR. JANUSH:

Q. I think it's going to be important to the court in this case as to whether you were citing literature that was concomitantly testing for acetaminophen use when assessing glutathione.

Is that a reasonable expectation, if -- if the court wants to see was the scientist actually looking at the right issue here?

MR. COHEN: Object to the form.

A. Depending on the question, it's a reasonable desire to see data specific to acetaminophen, but I would note that the plaintiffs' experts frequently rely on studies that have nothing to do with acetaminophen.

BY MR. JANUSH:

Q. But you're here today, and

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we're here to talk about you and your work.
You understand that, right?
MR. COHEN: Object to the form.
A. I'm here to talk about the questions that I was asked to address in my expert report.
BY MR. JANUSH:
Q. Uh-huh. And your work, right?
MR. COHEN: Object to the form.
A. I guess I'm not clear on what you mean by my work.
BY MR. JANUSH:
Q. Your expert report and your conclusions and your studies that you relied on is what is at issue today in front of this camera and in front of the court on this deposition, right?
MR. COHEN: Object to the form.
A. What is at issue today is the questions that I was asked to address in my expert report. I addressed them in the report.
BY MR. JANUSH:
Q. Meaning plaintiffs' experts are not in this deposition and they're not the

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subject of today's deposition, right?
MR. COHEN: Object to the form.
A. I think it's -- the -- my report is, in part, a response to the plaintiffs' experts. I think it's impossible to not cite them as a result of that or not discuss them. It's the basis of the report.
BY MR. JANUSH:
Q. I just want to conclude by coming back to a question I asked earlier and try and get a clean answer from you.
Would you agree that in this three-page Nitsche publication, the only endpoints being addressed were -- addressed were the measurements of acetaminophen observed in the fetus and observed in the mother following administration of the 1,000 milligrams of acetaminophen to the mother?
MR. COHEN: I'm just going to object to the colloquy at the beginning before the question --
MR. JANUSH: Fair enough.
MR. COHEN: -- which implied that he didn't give a, quote, clean answer. That was improper.

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A. So again, what's in the study is that they -- well, their conclusion from their data -- one of their conclusions from the data is that the plasma concentrations to which a fetus or neonate -- plasma concentrations of acetaminophen -- excuse me -- after a therapeutic dose ingested by the mother to which the fetus or neonate would be exposed is no greater than that to which the mother is exposed, right?
Given what we know about the lack of P4- -- lack of CYP2E1 in the brain, given what we know about the fact that there are no acetaminophen-protein adducts in the brain, even after massive overdoses of acetaminophen, given what we know about the fact that we have glutathione in the brain, including in the fetal brain, together with that information, these data suggest that acetaminophen would be safe to the fetus.
Again, that's the way I take the data. I cannot comment on how the authors themselves came to their conclusions.
BY MR. JANUSH:
Q. But you had -- fair to say you

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had no problem quoting their concluding sentence and not qualifying it as being unsupported within the four corners of the actual study itself, right, in terms of the design of the study?
MR. COHEN: Object to the form.
A. So when we do science, you never take it in isolation, right, unless there's just nothing else ever has been done on a particular subject. You always interpret it in the context of the literature.
BY MR. JANUSH:
Q. Except these scientists wrote "our findings," right? They weren't looking at other literature.
A. Again, they may have other studies. They may have meant our findings in terms of their results in the context of other things that they've found from other studies. I cannot comment on what they were thinking or their rationale for that statement.
Q. But you felt comfortable quoting it?

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MR. COHEN: Objection, form.
A. Yeah, I was comfortable quoting it because, again, when you take it in the context of the greater literature, it does strongly suggest that it's safe for the fetus. Or at least a neonate.
BY MR. JANUSH:
Q. I'm going to move on to paragraph 33, where you say: In the fetus, drugs also undergo metabolism. The human fetal liver expresses enzymes that can catalyze the sulfation of acetaminophen at levels that are comparable to the adult liver.
Dr. McGill, fair to say that this publication cited at 51, Hume, regarding sulfation of thyroid hormone and dopamine during human development, that --
A. I'm sorry. Footnote 51? I don't see a Hume.
Q. Richard K. Hume.
A. Oh. Hume is the second author.
Q. Okay. So Rich -- my apologies. I read that wrong. K. Richard with R. Hume.
Do you see that?

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A. I do.
Q. Okay. And fair to say this publication specifically concerns the role of sulfation of catecholamines and thyroid hormones during human development?
A. Again, to say definitively, I would prefer to see a copy of the actual study.
Q. We've marked this as 814.
(Whereupon, Deposition Exhibit P814, Sulfation of Thyroid Hormone and Dopamine during Human Development: Ontogeny of Phenol Sulfotransferases and Arylsulfatase in Liver, Lung, and Brain, by Richard et al., was marked for identification.)
BY MR. JANUSH:
Q. And it's titled, again, Sulfation of Thyroid Hormone and Dopamine during Human Development: Ontogeny of Phenol Sulfotransferases and Arylsulfatase in Liver, Lung and Brain.
(Document review.)
///

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BY MR. JANUSH:
Q. My questions may prompt a need for you to look at it further or may not, so I'd like to ask a question, and then you tell me whether you have to look at something specifically to answer it.
I appreciate that there's a conclusion or a statement on 2735 in the upper right-hand corner that says: To further our understanding of the role of sulfation of catecholamines and thyroid hormone during human development, we have studied the ontogeny of the SULT and ARS isoenzymes involved in their metabolism in key tissues, liver, lung and brain, using isoform-selective probe substrates and immunochemical techniques. Our data strongly support the idea that the human fetus has an extensive capacity for sulfation, and we demonstrate for the first time a developmentally programmed switch in the hepatic expression of the major catecholamine-metabolizing sulfotransferase, SULT1A3.
Do you see that?

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A. Yes.
Q. In this study, weren't tissues obtained from postmortem within 12 hours of certification of death?
A. I'd have to double-check the methods.
Q. Please do.
(Document review.)
A. So it states: Tissue was obtained from fetuses within six hours following termination of pregnancy. Infant tissue was obtained at routine postmortem within 12 hours of certification of death.
BY MR. JANUSH:
Q. Okay. Did any aspect of this study address the relevance between APAP sulfation or acetaminophen sulfation and sulfation of iodothyronines or thyroxine T4, a prohormone secreted by the thyroid?
A. I'm sorry, can you ask the question again? I want to make sure I understand.
Q. Yeah.
Did any aspect of this study address the relationship between

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acetaminophen sulfation and sulfation of thyroxine T4?

A. Right. So they actually look at multiple sulfation substrates, right? One of those -- let's see if I can find it again here.

So -- so -- I'm sorry, on the first page, 2734, the right-hand column, close to the top -- I think it's the second sentence. They state: Human SULT enzymes can be subdivided, based on amino acid sequence identity and enzymatic function, into phenol SULT, SULT1, and steroid SULT, SULT2, families, where the SULT1 family comprises enzymes metabolizing phenolic xenobiotics and iodothyronines and catecholamines.

So you can see there that they are pointing out that they're interested in SULT1A family, correct? Acetaminophen is metabolized by members of the SULT1A family of sulfotransferases.

In addition, one of the substrates that they use -- they don't just use the substrates that you mentioned. For

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example, just one example, they also look at sulfation of 4-nitrophenol, which they seem to use as a marker of SULT1A1. And again, SULT1A, sulfotransferases are involved in acetaminophen metabolism.

And if I can find that one statement again.

(Document review.)

BY MR. JANUSH:

Q. What I'm addressing, though, is: Did this study actually review acetaminophen?

A. I don't recall if they specifically mentioned acetaminophen in this paper or not.

Q. Why don't you look through it.

A. You --

Q. You had a few minutes before to look through it.

A. You'd like me to read the entire paper?

Q. Well, just -- you can just scan it. I want to confirm whether you cited a paper that has nothing to do with acetaminophen.

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A. Well --

Q. I get what you're saying about SULT1 and all that, but I'm addressing whether acetaminophen sulfation was tested in this paper.

A. I don't believe they specifically looked at acetaminophen sulfation. Again, however, this is standard practice in the field, right? You use well-characterized substrates to look at enzyme activity, and especially drug-metabolizing enzyme activity.

And so again, acetaminophen is known to be sulfated by members of the SULT1A family, and they have shown SULT1A activity here.

Q. But not shown acetaminophen in this entire study, right?

A. Not specifically, but the results are suggestive that there is acetaminophen sulfation.

Q. Well, SULT1 sulfation is broader than acetaminophen sulfation, isn't it?

A. True.

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Q. Yeah. How much broader?

A. I -- I mean, I'm not sure how to answer that question.

Q. Well, what does SULT1 sulfation entail beyond acetaminophen sulfation?

A. I'm sure it sulfates other drugs and some other chemicals as well.

Q. So what led you to speculate that you're sure that acetaminophen was relevant here?

MR. COHEN: Object to the form.

A. Let me find. So I -- let me -- which part -- I'm sorry, can you remind me what -- which part of the expert report you're referring to? Oh, I see it. I'm sorry. Paragraph 33.

BY MR. JANUSH:

Q. 33.

A. So they express enzymes that are -- that can or, in other words, are capable of sulfation of acetaminophen, and that's what they've shown here. These are enzymes -- they're testing enzymes that are -- that can sulfate acetaminophen.

In addition to that, I have

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additional references in that footnote, one of which, at least, does specifically address acetaminophen.

Q. Let's turn to paragraph 34 on page 26. And here you're addressing the blood-brain barrier.

Dr. McGill, as part of your report in this case, are you opining that acetaminophen does not cross the fetal blood-brain barrier?

A. No.

Q. Okay. You don't know what amount of acetaminophen is getting into the fetal brain at various stages of pregnancy, right?

A. At various stages of pregnancy? I don't recall specifically if any of the studies I cited looked at that, getting into the fetal brain at various stages of pregnancy.

Again -- well, the short answer is no, but we do know how much is in the fetal plasma, and it can't be more than that.

And the amount in the fetal plasma, by the way, one example of that comes

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from the study that we were discussing a moment ago, looking at that neonatal exposure, and they showed that the concentrations and the -- well, at least the neonatal samples and the cord blood samples were the same as in the mother, concentrations of acetaminophen.

And again, because acetaminophen is a weak acid, a pKa of about 9.5, it's uncharged and not very polar at physiological pH, which means it can cross in brains fairly freely. There's a delay with the blood-brain barrier, but it can cross. And so there's no reason to believe that it would accumulate in the brain, and so -- including the fetal brain.

And so we can assume that whatever concentration is in the fetal brain at any stage of fetal or embryonic development, it's no greater than what's in the plasma.

Q. I want to focus on some particular statements you make in this paragraph.

Similar to the results in

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humans, maximum acetaminophen concentrations were far lower in the brain extracellular fluid than in plasma in these animals. These data show that the blood-brain barrier delays entry of acetaminophen into the brain, keeping peak concentrations lower in the brain than in plasma.

Although these studies were performed in adult humans and animals, it has been demonstrated that the blood-brain barrier is intact in the human embryo/fetus by approximately 8 weeks of gestation, and functional by 10 to 12 weeks.

Then you have a comma and a footnote, 56 -- indicating that the fetal brain is also protected. And you have footnote 57. And we're going to go through each footnote 56 and 57.

But before I do that, I'll just address initially:

You cited literature at footnote 56 by Kate Goasdoué, Stephanie Miller, Paul Colditz and Tracey Björkman, a Review: The blood-brain barrier, protecting the developing fetal brain.

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Do you recall if there's anything about acetaminophen in this review?

A. Off the top of my head, I do not recall.

Q. Okay. Would it surprise you if there was nothing about acetaminophen in this review?

MR. COHEN: Objection, form.

A. No, because I'm not citing this review as evidence for whether or not acetaminophen crosses the blood-brain barrier. I'm just citing it as a source for the statement that the blood-brain barrier is intact by 10 to 12 weeks' gestation.

This citation was not intended to say anything about acetaminophen.

BY MR. JANUSH:

Q. Did you misrepresent what Goasdoué et al. actually said in their publication?

MR. COHEN: Objection, form.

A. I don't believe so.

BY MR. JANUSH:

Q. Let's walk through it.

THE STENOGRAPHER: Is this a

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new exhibit?
MR. JANUSH: This is exhibit P815.
(Whereupon, Deposition Exhibit P815, Review: The blood-brain barrier; protecting the developing fetal brain, by Goasdoué et al., was marked for identification.)
BY MR. JANUSH:
Q. We're going to go to Section 8, Conclusion. We're going to blow this up. I'm going to read it.
Despite the presence of placental efflux transporters, the placenta is an imperfect drug barrier. Given sufficient time and dosage, most drugs can breach the placenta and enter the fetal circulation, posing a teratogenic risk to the fetal brain.
Let me stop there for a second. Is a teratogenic risk to the fetal brain a good thing or a bad thing?
MR. COHEN: Object to the form.
A. A risk is a risk. It doesn't mean that something happens, for starters.

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Second of all, my statement is about the blood-brain barrier. This is about the placental barrier. They mention the brain, but they're not discussing that in this sentence.
BY MR. JANUSH:
Q. I'm not done. I have a lot more to go.
Although the placenta and blood-brain barrier have several efflux transporters in common, the blood-brain barrier is a far more structurally complex and restrictive system. To cross the blood-brain barrier and enter the central nervous system, drugs need to be small and lipophilic or have dedicated transport systems.
Drugs with these properties would easily cross the placental barrier even with functional efflux transporters, as quick diffusion surpasses the ability of efflux transporters to pump substances from the fetal circulation. Understanding how the blood-brain barrier functions during development of the fetus is essential to

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ensuring optimal brain growth and protection from drugs and toxins once they cross the placenta.
Given the differences in blood-brain development -- blood-brain barrier development across species, refinement of animal models is critical before application to the human.
So far I've read that correctly, right?
A. Yes. As far as I've been able to keep up, yeah.
Q. Well, please stay with me and let me know if I'm losing you because the next sentences are really critical to this case and to this article.
Minimizing drug exposure in the fetus is vital to reducing teratogenic effects and long-term neurological disease.
You ignored that statement when you cited to Goasdoué, right?
A. No. Again, I cited this article as support for my statement that the blood-brain barrier is intact by 10 to 12 weeks' gestation. I didn't make any

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comments in referencing that article about teratogenicity, drug exposure. I just said the blood-brain barrier was intact.
Q. Okay. That's actually, by the way, not so true either, right? A -- by 8 weeks of gestation and functional by 10-12 weeks -- 10 to 12 weeks -- is your statement in your report in terms of the timeline for a blood-brain barrier to be intact.
But isn't it scientifically established that the blood-brain barrier continues forming and becoming tighter throughout gestation and even continues to develop postnatally?
A. I'm not an expert on blood-brain barrier development. I'm just citing what I found in those two articles.
Furthermore --
Q. But this case --
A. Sorry. Go ahead.
Q. This case is --
MR. COHEN: I'm sorry, were you finished?
MR. JANUSH: Yeah.
A. Yeah, furthermore, I don't

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dispute anywhere in my report that acetaminophen crosses the blood-brain barrier. I guess I don't -- I don't dispute that.

BY MR. JANUSH:

Q. Do you agree that it crosses the blood-brain barrier and can cause teratogenic effects to the fetus?

MR. COHEN: Objection, form.

A. That acetaminophen can cross the blood-brain barrier and cause teratogenic effects? I mean, I've seen no data that indicates that. No reliable, reproducible, scientifically rigorous data that indicates that.

BY MR. JANUSH:

Q. And again, you haven't produced your methodology concerning your searches and how you arrived at the literature you selected to review for your report, right?

MR. COHEN: Objection, form.

A. I think I explained my methodology pretty clearly this morning. Again, I used the scientific method. I'm happy to --

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BY MR. JANUSH:

Q. No, we're not doing that again.

MR. COHEN: Well, let the record reflect you asked and you cut him off.

BY MR. JANUSH:

Q. And let's go to the next paragraph: A significant clinical challenge is the protection of the vulnerable fetal brain from drugs in the maternal environment. The changes in placental or blood-brain barrier function due to drug exposure from the maternal environment have significant clinical relevance as the functional outcomes vary and are often unknown.

As you sit here today, do you agree with this statement?

A. Again, I'm -- I'm not an expert on blood-brain barrier development, and this is not what I study, so I -- I really -- I can't comment.

Q. But you included a section in your report specifically addressing the blood-brain barrier, right?

A. I mentioned that the

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blood-brain barrier is -- based on the references that I cited, is intact during certain -- by a certain point in the embryonic or fetal development.

I also discussed acetaminophen pharmacokinetics in the CSF. In order to get to the CSF, it must cross the blood-brain barrier. And I am an expert in acetaminophen metabolism and pharmacokinetics, so I can address that.

I'm not an expert in blood-brain barrier development or this specific question about maternal environment. That's not my expertise.

Q. Okay. And now I promised we'd get to the next footnote. I've only addressed Goasdoué at 56, after you say: Although these studies were performed in adult humans and animals, it has been demonstrated that the blood-brain barrier is intact in the human embryo and fetus by approximately 8 weeks of gestation and fully functional by 10 to 12 weeks.

You address, quote: indicating that the fetal brain is also protected.

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That's -- that's a statement, right? You're indicating -- are you indicating -- you are -- let me -- let me ask this question differently.

Is this your work or someone who wrote this for you?

MR. COHEN: No, no, no, no. Stop.

A. I wrote the report.

MR. COHEN: Stop. Stop.

BY MR. JANUSH:

Q. You wrote the report.

MR. JANUSH: So no, I'm --

MR. COHEN: I know you didn't do it intentionally, but you said "fully functional" and the word "fully" is not there.

MR. JANUSH: I did not mean that. You are correct. Thank you.

MR. COHEN: Thank you.

BY MR. JANUSH:

Q. So you are, in the first portion of this sentence preceding the comma, addressing that the blood-brain barrier has been demonstrated to be intact by

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approximately 8 weeks of gestation and fully functional by 10 to 12 weeks.

MR. COHEN: No.

BY MR. JANUSH:

Q. And then concluding, indicating that the fetal brain is also protected, cite footnote 57, Bell/O'Shaughnessy publication.

MR. COHEN: Object to the form.

Go ahead and answer, but he didn't mean fully.

MR. JANUSH: Oh, sorry. I said it again?

MR. COHEN: Yes.

MR. JANUSH: We'll delete "fully" from the record.

MR. COHEN: It's fine.

MR. JANUSH: "Functional" is what I meant. You are correct.

BY MR. JANUSH:

Q. Okay. So my question is: Did you actually read the citation at footnote 57? Did you read that, that piece of literature?

A. Yes.

Q. You did?

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A. Uh-huh.

Q. Do you remember it?

A. I mean, it's been a little while since I looked at it. I don't recall every detail off the top of my head.

Q. Do you remember what was being studied in this piece of literature called The development and function of the brain barriers - an overlooked consideration for chemical toxicity?

A. If my recollection is correct, it was a review. I don't think it was a study.

Q. Do you know what contaminants were being reviewed?

A. Off the top of my head, I don't recall.

Q. What does "biological plausibility" mean?

A. So when something -- in order for something to be biologically plausible, at least, you know, my definition, in order for something to be biological plausible -- biologically plausible, excuse me -- you have to have a firm mechanism that has been

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established through a body of literature describing rigorous, reproducible scientific studies.

Q. So I'm going to give you a different definition and see if you agree.

Would you agree that biological plausibility concerns whether the hypothesized causal link is credible in light of what is known from science and medicine about the human body and the potentially offending agent?

A. I dislike the term "causal link," and I -- I would qualify -- so I would -- I would say that there has to be a firm mechanistic link, as I said, a well-established mechanism.

And in terms of how we define credible, again, that's referring to my statement of -- or I would say that that's related to what I said about needing to have studies that are rigorous and reproducible.

Q. You cited a publication at footnote 57 for the concept that the fetal brain is protected by the blood-brain barrier, right?

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A. First of all, when I say protected here, I'm not saying that it prevents acetaminophen from crossing the blood-brain barrier, right? Actually, in other parts of this paragraph, I state that if you look at overall exposure, the AUC, there's a one-to-one relationship between plasma and CSF, which means that the acetaminophen gets in there, right? It just has delayed entry. And that's what the studies I've cited in rodents and humans show.

So I want to be careful about how we're using the word "protected."

In addition to that -- so you're asking me that's what I've cited to show that?

BY MR. JANUSH:

Q. You cited this article, this --

A. Right.

Q. -- specific publication to demonstrate that it indicates that the fetal brain is also protected, right?

A. Yeah, from people who have reviewed the literature on that -- the

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relevant literature on that topic.
Q. Okay. So let's -- let me show you what you considered the relevant literature on this topic. It's P816.
(Whereupon, Deposition Exhibit P816, The development and function of the brain barriers – an overlooked consideration for chemical toxicity, by Bell et al., was marked for identification.)
BY MR. JANUSH:
Q. The development and function of the brain barriers - an overlooked consideration for chemical toxicity.
I'm going to just ask you a simple question at the outset: Can you identify what contaminants -- what two contaminants were being addressed in this entire study as it concerns the blood-brain barrier? And I think it's in the closing remarks at page 19.
A. So without reading through it again, I would not be comfortable saying for sure what two. I can tell you two that I see right away.

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Q. PFAS and bisphenol, right?
A. Those are the two that I see right away. I can't say if there are any others. I'll have to take your word for it.
Q. Well, I'll make you a deal so we don't take up a lot of time. You get a chance to issue an errata if PFAS and bisphenols are not the only two chemicals being studied in this -- in this piece of literature for purposes of analyzing the blood-brain barrier.
MR. COHEN: We're not making deals. Sorry, just ask your questions.
MR. JANUSH: Then I can go off the record and have him review it on his time and tell me if PFAS and bisphenol are the only two.
MR. COHEN: No --
MR. JANUSH: Actually, you know what? I'm going to make him do this on video because I think this is going to be painful.
BY MR. JANUSH:
Q. So let's go through the report,

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and find me where acetaminophen is addressed anywhere within this piece of literature addressing the protection of blood-brain barriers.
MR. COHEN: That's a different question. So ask that question.
MR. JANUSH: I did.
A. If you would like to do that, we can do that.
BY MR. JANUSH:
Q. I'd like for you to find where -- find me where acetaminophen is addressed in this report, unless you know the answer --
A. But I --
I'm sorry, I interrupted you. I'm sorry.
Q. Unless you know the answer already and you know that this is a bisphenol and PFAS study only, which I think you know.
A. Okay. A couple of things. First of all, it's not -- this is not a study, right? It's a review of the literature that cites multiple other studies.
In addition to that, I don't

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see the relevance because I have not disputed that acetaminophen crosses the blood-brain barrier. In fact, I've said that it does, and I've cited data showing that it does in my report.
When I've used the word "protected," as I stated just a moment ago, we need to be careful how we're using it. Perhaps I used it a little inartfully in that sentence. When I used that word, what I was referring to was the delay in entry of acetaminophen to the CSF, and therefore, the brain compartment.
Q. But, Doctor --
A. What that delay -- if I may finish.
Q. Yeah. I didn't mean to interrupt there.
A. What that delay means is that the maximum peak concentrations achieved in the CSF are lower even than the plasma concentrations, the maximum peak plasma concentrations.
So what that means is that at one point in time, the brain is always -- or,

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generally speaking, exposed to less than the rest of the body.
Q. Are you --
A. So -- I'm sorry. Go ahead.
Q. Are you aware that bisphenol is about 100 grams per mole heavier and larger than acetaminophen?
A. I don't know all the chemical properties of -- first of all, there are multiple bisphenols, right? There's not just one. I don't know all the chemical properties of all of them.
Q. Are you aware that PFAS is about three times larger than acetaminophen, from a molecular size and weight?
A. Once again, PFAS stands for perfluorinated alkylated substances. This is a large group of chemicals that have multiple different properties. I don't know the characteristics of every single one of them.
Q. If you looked at toxicants in this report that are two and three times larger than acetaminophen to conclude that acetaminophen -- that the fetal brain is also protected from acetaminophen, that would be a

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bad thing, right?
MR. COHEN: Objection, form.
A. Again, I did not dispute that acetaminophen crosses the blood-brain barrier. In fact, I said that it does.
BY MR. JANUSH:
Q. But you said that the fetal brain is protected, right?
MR. COHEN: I don't think he was finished.
MR. JANUSH: Sorry.
A. What -- again, what I meant by the word "protected" is that there is a delay in entry through the blood-brain barrier, and that is not just me claiming that. This is not the study that shows that.
This is a study in which, if memory serves correctly, they just mentioned that the blood-brain barrier might protect against some chemicals, right? The studies that show the delay in entry are --
(Telephonic interruption.)
THE WITNESS: I'm so sorry. I meant to silence my phone. I apologize for that.

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MR. COHEN: Do you need to take a break?
THE WITNESS: I can finish my answer.
MR. COHEN: Yeah, finish your answer. We've been going over an hour anyway, so...
THE WITNESS: Okay.
A. So, I'm sorry, let me -- so when I use the term "protected," I'm referring to the delay of entry into the brain across the blood-brain barrier. That is demonstrated in the two studies that I cited above, the human study as well as the rat study.
Because again, when you look at the data in those studies -- which I'm happy -- if you want to produce the paper, I'll show it to you. They see that the acetaminophen enters there a bit more slowly, and that's why the peak CSF concentrations of acetaminophen are roughly half or less than the peak plasma concentrations of acetaminophen at therapeutic doses.
So again, that's what I mean

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when I use the term "protected." I'm not saying acetaminophen doesn't cross the blood-brain barrier.
BY MR. JANUSH:
Q. Dr. McGill, when you're saying in your report that the blood-brain barrier is intact in the human embryo/fetus by approximately 8 weeks of gestation and functional by 10 to 12 weeks, indicating that the fetal brain is protected, you've cited for the protective component of that sentence the Kiersten Bell publication we're going over, right, this PFAS and bisphenol publication? That's all I'm addressing.
A. So you have to take it in the context of the data above, right? Again, as a scientist, you don't interpret data in -- or don't interpret statements or data in isolation.
The studies above show that in adult humans and in rats, there's delayed entry of acetaminophen across the blood-brain barrier, which reduces the maximum CSF concentration that's achieved.
We don't have specifically data

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for crossing the blood-brain barrier in the embryo or fetus. In the absence of that data, all we can really do is say, okay, well, might this happen in an embryo or fetus? Well, if they have a blood-brain barrier intact, then it might happen.

So that's -- those are the statements that I'm making in this part, and that's what the citations support.

Q. How --

A. The data showing the delayed entry are in the citations above that.

Q. If Judge Cote were reading your report, how would she know all of that extra explanation of what you meant based on the words you actually did include here?

MR. COHEN: Objection to the form.

A. Again, I have cited these data above.

BY MR. JANUSH:

Q. Yeah. But, Dr. McGill --

A. I --

Q. -- holding it up --

A. I think it's clear, and --

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MR. COHEN: Let him finish.

A. -- maybe there can be a matter of disagreement over my writing style. I felt it was clear.

BY MR. JANUSH:

Q. I understand that you felt it was clear, but you -- you footnoted that the fetal brain is also protected by citing to a PFAS and bisphenol study where both of those toxicants are significantly larger than acetaminophen.

And so I'm asking you whether that was an intellectually honest scientific conclusion.

MR. COHEN: Object to the form.

A. Yes, when you understand the way that I defined "protected" and that this is -- statement is based on terms of data on the studies that I cited and described above. When you interpret it in the context of the report, yes, this is absolutely an accurate statement.

BY MR. JANUSH:

Q. Okay. You also --

MR. COHEN: So --

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MR. JANUSH: Just one more question.

MR. COHEN: Yeah, yeah.

BY MR. JANUSH:

Q. You also -- but you appreciate, do you not, that the size -- the size of the molecule has everything to do with what passes through the blood-brain barrier, how quickly, how easily, and at what particular point of gestation, right?

A. So again, the size is one factor. There's also the actual chemical properties of the drug. As I described -- and again, I'm not disputing that acetaminophen crosses the blood-brain barrier.

Acetaminophen is much smaller, yeah. It's at physiological pH, around 7.4. It's a weak acid with pKa 9.5, so it's uncharged at physiological pH, and it's lipophilic enough that it crosses the blood-brain barrier. I have not disputed that.

Q. So what was the protection that you were citing to at footnote 57?

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A. Excuse me, I'm sorry, I didn't mean to interrupt.

As I've stated multiple times now, when I said "protected," I'm referring to the delay in entry to the blood-brain barrier. We have empirical evidence for that. That's shown in the two studies that I cited above, above these statements.

MR. COHEN: Good time for a break?

MR. JANUSH: Sure.

MR. COHEN: Thank you.

THE VIDEOGRAPHER: We are going off record. The time is 3:01.

(Recess taken, 3:01 p.m. to 3:23 p.m. CDT)

THE VIDEOGRAPHER: We're going back on record. The time is 3:23.

BY MR. JANUSH:

Q. Dr. McGill, one of the key opinions in your report concerns the excess NAPQI hypothesis; is that correct?

A. I discuss the excess NAPQI hypothesis.

Q. Is it not one of the key

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opinions in your report?
A. I haven't heard an opinion in the question.
Q. The opinion you offer on the excess NAPQI hypothesis is -- sorry, I'll ask it differently. I'll ask it differently.
At paragraph 39, you address: The liver contains a large amount of CYP2E1 enzyme that can generate NAPQI, and it encounters more acetaminophen than other organs due to first-pass metabolism. Yet, because of the presence of glutathione, an overdose of acetaminophen of around at least 10 grams in a single dose is required to cause clinically significant liver injury. Therefore, to establish the biological plausibility of plaintiffs' experts' hypothesis that maternal ingestion of recommended dose, maximum of 1 gram, of acetaminophen causes developmental neurotoxicity through NAPQI expression in the embryonic/fetal brain, it must be demonstrated that, (a) CYP2E1 enzyme is present in the embryonic/fetal brain at levels that are at least comparable to the

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liver, and (b) embryonic/fetal brain glutathione concentration is insufficient to detoxify any NAPQI that may be produced.
Is that one of the key opinions you offer in your report?
MR. COHEN: Objection, form.
A. It is -- how to say that. It's not a conclusion. It is what you would have to show in my opinion to demonstrate -- I mean, to do what I've written here.
BY MR. JANUSH:
Q. Yeah, I understand that you didn't address yet what's been demonstrated, but those are -- those two functions, (a) and (b) of paragraph 39, you believe plaintiffs must demonstrate; is that right?
A. Yes.
Q. What published literature do you rely on for the proposition that to establish maternal ingestion at recommended doses causes neurotoxicity through NAPQI expression in the embryonic/fetal brain it must be demonstrated that CYP2E1 enzyme is present in the embryonic/fetal brain at levels that are at least comparable to the

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liver?
A. It's extremely well established through many, many studies over the last 50 years that you have to have an overdose of acetaminophen to have clinically significant liver -- liver entry, right?
The liver has a lot of P450, and so in order for -- so we know, right, that an organ with a lot of P450 requires this overdose, roughly an overdose in this range of 10 grams in a single dose, in order to develop toxicity. So --
Q. So -- okay. Sorry.
A. So certainly you wouldn't expect toxicity in another organ that doesn't have as much CYP2E1, certainly not at therapeutic doses.
Q. Can you point me to a piece of scientific literature saying that a baby in utero needs -- a fetus in utero needs at least comparable levels of CYP2E1 enzyme in the brain as they would have in the liver?
A. Again, therapeutic doses don't cause toxicity in the liver. Only overdoses do. The liver has an enormous amount of

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CYP2E1. If you had any less CYP2E1, well, if you don't get injury at therapeutic doses in the liver and you have even less CYP2E1, then you're not going to get injury in that organ with less CYP2E1.
Q. I'm going to ask it again.
Can you point me to any literature that supports the opinion that plaintiffs must demonstrate that CYP2E1 enzyme is present in the embryonic/fetal brains at levels that are at least comparable to the liver?
A. Sorry, I think your question is -- you're asking me if there are -- can I point you to literature that shows there are comparable levels of CYP2E1 in the brain to the liver? Sounds like that was your question this time.
Q. You're saying --
A. There are no --
Q. -- for us to establish biological plausibility, can you establish -- can you point me to any literature that supports that we would need to show that plaintiffs would need to show this, this

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standard that you've set?
A. There -- again, there is 50 years of data showing numerous studies, including many that I've cited in my report, that therapeutic doses of acetaminophen do not cause liver injury. The liver has an enormous amount of CYP2E1, so if you have an organ with even less CYP2E1, you are certainly not going to get therapeutic injury with therapeutic doses in that organ.
Q. Sorry. You are -- you are addressing that we need to show -- plaintiffs need to show that CYP2E1 enzyme is present in the brain at levels at least comparable to the liver in order to establish biological plausibility that acetaminophen causes developmental neurotoxicity through NAPQI expression, right?
A. My statement is that in order for -- to establish the biological plausibility, right, that maternal ingestion of recommended doses of acetaminophen could cause neurodevelopmental toxicity, you would need to have, at a minimum, the amount of CYP2E1 in the brain that you find in the

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liver.
Q. What literature do you cite to -- what can you point plaintiffs to and the court to to support that statement? That's all I'm asking.
A. Okay. So again, there's 50 years of literature. If you'd like me to give you one example, you can look at my 2013 study where I'm the first author. That would be this study, which I believe you marked as Exhibit P803.
Q. Uh-huh. Let's pause with that one, okay. We'll talk about that one.
MR. COHEN: What's the number?
MR. JANUSH: P803.
BY MR. JANUSH:
Q. Doesn't P803, your own literature, conclude that you were able to detect protein binding after treatment with 15 milligrams per kilogram of APAP at earlier time points with only minimal loss of liver GSH, glutathione?
A. As we discussed earlier, again, protein adducts are necessary but not sufficient for toxicity; protein adducts

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don't cause toxicity. And again, when I used the term "minimal," this is relative to the other doses in the study. Again, you can look at Figure 2A and you can still see that there was loss of glutathione, even at that very low dose.
Q. But here's the problem. You didn't study what concurrent treatment, what constant chronic therapy on acetaminophen over a period of time at recommended doses would do to address protein binding in a brain.
You're a single-overdose liver scientist, and that's what you've presented in your report by and large.
A. As I've --
MR. COHEN: Objection, form.
Go ahead.
A. As I've discussed earlier in the day, the plaintiff experts also rely on studies of single acute overdoses, and what we know about -- when you take multiple doses of acetaminophen -- I stated this in my report -- is that the steady-state plasma concentration is around 50 micromole per

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milliliter, which is very low. That's a concentration that doesn't cause any kind of toxicity in the liver.
And so some of the reports discussed by Dr. Louie where they might purport to provide data on longer exposures to acetaminophen, or where at least Dr. Louie, for example, interprets the data that way, they're looking at concentrations that are far higher than that.
BY MR. JANUSH:
Q. What's the amount of protein binding in the fetal brain that would be problematic?
A. I can't say. I mean, I can tell you what we typically see in the liver, which, I mean, you can --
Q. Would you agree liver injury is not equal to brain injury, right?
A. That's quite a broad statement. Again, the hypotheses that I'm addressing about NAPQI, protein binding in the brain, they come from the plaintiffs' experts, and that's what I've been asked to address. And they -- the plaintiffs' experts derived them

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from what happens in the liver.
Q. But when seeking to cite to literature that supports your report, you cited me to your own literature from 2013, right?
A. So again, what we see in the liver, and again, the plaintiffs' experts are giving their hypotheses that I'm simply addressing from data in the liver, so that's the context that we're working in, right? What we see in the liver is that you have extremely high CYP2E1 levels, and you still have no toxicity at therapeutic doses ever -- or at least clinically significant liver injury. Let's put it that way.
So if you have an organ with even less CYP2E1, then certainly therapeutic doses would not be expected to cause injury within the framework that has been established by the plaintiffs' experts to which I am responding.
Q. Is it your opinion that because at least 10 grams in a single dose of acetaminophen is required for liver injury, that similar levels of glutathione depletion

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are necessary to trigger developmental neurotoxicity through NAPQI expression in the embryonic or fetal brain?
A. Again, we're working off of what we know in the liver, which is the framework that the plaintiffs' experts have provided. Based on what we know happens in the liver, which the plaintiffs' experts reference, I would assume that you would have to have extensive GSH depletion, glutathione depletion.
Q. In your literature at P803 that we have before us, haven't you published -- haven't you included statements concluding that a greater than 70% reduction is not necessary -- and we're talking about glutathione reduction -- is not necessary for NAPQI-induced hepatotoxicity?
A. No, I have not.
Q. I might have the article wrong, but let me see.
What this article does say, however, is that binding to proteins, and mitochondrial proteins, causes oxidative stress and mitochondrial damage resulting in

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necrotic cell death.
You agree with that, right?
MR. COHEN: I'm sorry, which page are you on?
MR. JANUSH: Introduction.
A. In the liver after overdose.
BY MR. JANUSH:
Q. And you also address that protein binding APAP-CYS could be detected in serum from humans after only therapeutic doses, citing to Heard, right?
A. Yeah. Again, protein binding is necessary but not sufficient for toxicity.
Q. Well, if protein binding occurs over an extensive period of time, have you considered what the impact would be when someone is -- a maternal -- a pregnant woman is taking Tylenol or acetaminophen on a daily basis, multiple doses throughout the day?
MR. COHEN: Objection, form.
Go ahead.
A. So what you're -- what you seem to be suggesting or that my interpretation is that formation of more adducts over time would cause greater injury, so actually, we

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have done -- well, let me rephrase that.
I'm aware of studies -- at least one study that has been done where I believe they did look at multiple dosing of acetaminophen, even at actually fairly high doses, but still sub-hepatotoxic, and they didn't find any evidence of toxicity.
Regardless, even --
BY MR. JANUSH:
Q. Is that study cited in your report?
A. I -- I don't recall for sure, but I don't believe I stated that one.
Q. Why not?
A. Well, your --
Q. Given that this isn't a single-use overdose case, why not?
A. So it's -- it's not a study of therapeutic dosing, and --
Q. Nor are your single-use overdose cases, right? Those case reports and the published literature are not therapeutic dosing, are they?
MR. COHEN: Objection, interrupted the witness.

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Go ahead.
A. So -- right. If you're concerned about single dosing and overdosing, again, the plaintiffs' experts rely on the same kinds of studies for their opinions.
I mean, in addition to that, that's where most of the data on acetaminophen toxicity come from, so we kind of have to rely on it.
But there are studies of long-term therapeutic dosing in humans, and they never show clinically significant liver injury that's clearly due to the acetaminophen.
BY MR. JANUSH:
Q. Dr. McGill, for a while today we've addressed the notion that you've published, including at footnote 803 -- excuse me, Exhibit 803, that protein binding can occur without much loss of GSH, right?
A. Again, this is a -- there is loss of GSH. Minimal or much loss of GSH in my paper that we've discussed was a relative term compared to the other doses, the overdoses. There's still loss of GSH.

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Q. And the protein binding we are addressing in this article is NAPQI expression, right?
A. The protein adducts that form are a result of NAPQI reacting with proteins.
Q. Dr. McGill, you also claim that there's an immediate detoxification of NAPQI in the brain due to the presence of glutathione, right?
A. Can you point me to that statement that you're quoting?
Q. I'm just saying you claim that, that the brain would detoxify any NAPQI present because the brain has sufficient NAPQI to detoxify -- sufficient --
A. Yeah, I --
MR. COHEN: Wait, wait.
MR. JANUSH: Excuse me.
THE WITNESS: Sorry, I should not have interrupted.
MR. COHEN: Let him --
Will you start the question again? It got interrupted.
BY MR. JANUSH:
Q. I mean -- that the brain has

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sufficient GSH, is what I meant to say, that the brain has sufficient GSH to detoxify any NAPQI that would be expressed. That's what I meant to say.
You take that position, right?
MR. COHEN: Objection, form.
A. We know from the studies that I've cited in my report on glutathione levels in humans that the brain, including the fetal brain, possesses millimole per liter concentration of glutathione.
Considering you only have micromole per liter -- so on the order of a thousand-fold lower concentrations of acetaminophen in the plasma, and only a small portion of that ever gets converted to NAPQI, I think it's very safe to say that there's sufficient glutathione in the brain to detoxify -- including the fetal brain -- to detoxify any NAPQI that might be formed there.
Again, there's absolutely no evidence for NAPQI formation in the brain even after massive overdoses of acetaminophen. Individuals, other groups

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have looked at that, acetaminophen-protein binding, as a surrogate for NAPQI formation. They do not find any evidence for it.
And -- well, I'll just leave it at that.
BY MR. JANUSH:
Q. At paragraph 41, you wrote: According to this database -- and the database that you are addressing is the Human Protein Atlas database -- the adult human brain has less than one-seven-hundredth of the CYP2E1 mRNA than in the adult liver, even using the highest value in the brain measured in the cerebellum. Even if small amounts of mRNA are detected, the corresponding protein might not be made from the mRNA (i.e., expressed).
And you also address that there's no indication in their data with respect to the database that CYP2E1 is more highly expressed in the brain during development compared to adulthood, right?
A. Yes.
Q. Just because something appears in a smaller amount doesn't mean that it

fails to present clinical manifestations, right?

A. In the case of a -- in this case it does because, again, you don't have -- right, okay. We're working with the liver here because that's where we have most of our data, okay, on acetaminophen toxicity. It's also the framework established by the plaintiffs' experts.

We know in the liver, at therapeutic doses, you do not get clinically significant liver injury. The liver has an enormous amount of P450. If you find that there's another organ that has less P450, specifically less CYP2E1, then you certainly would not expect therapeutic doses to cause any injury there.

Q. I'm going to present to you the Bhamre article as P818.

(Whereupon, Deposition Exhibit P818, Purification of Multiple Forms of Cytochrome P450 from a Human Brain and Reconstitution of Catalytic Activities, by Bhamre et al., was marked for identification.)

BY MR. JANUSH:

Q. Now, you address Bhamre and claim that: Bhamre reported virtually no CYP2E1 immunoreactivity on immunoblots of cytochrome P450 fractions purified from a male human brain; is that right?

A. Yes.

Q. Okay. So in the study, the brain that was being analyzed was 11 hours postmortem, right?

A. Sorry. Just to clarify your prior question, you did say CYP2E1 immunoreactivity, correct, specifically?

Q. I said CYP2E1 immunoreactivity.

A. Just to be sure that's what we're talking about.

Q. Immunoblots of cytochrome P450 fractions purified from a male human brain.

A. Yes, CYP2E1 immunoreactivity in those fractions.

Q. Yeah. So this was a decedent from a motor vehicle accident having donated their brain, apparently, and the brain is being studied 11 hours postmortem, right?

A. That's what they state here.

Q. Can you point anywhere in this article where there's a reflection that there was acetaminophen use?

A. This is not a study of acetaminophen, nor did I cite it as such, right? I cited this as evidence that there's no CYP2E1 in the brain --

Q. I get that.

A. -- in the human brain.

Q. I understand that.

But isn't acetaminophen -- doesn't acetaminophen induce CYP2E1? Isn't CYP2E1 highly inducible due to acetaminophen?

A. No.

Q. You disagree that -- you don't believe CYP2E1 is inducible?

A. I do not. No, no, let me rephrase that. CYP2E1 is not inducible by -- well, there is no clear reproducible, rigorous evidence that acetaminophen induces CYP2E1.

Q. Interesting.

A. In fact, there's conflicting data, for example, Bao 2020, which actually shows, when you look at messenger RNA protein

level and CYP2E1 activity in the brain of mice at different ages, what they find consistently is a decrease, in fact, in CYP2E1 levels in the liver.

Q. So I'm going to turn back to that later. We're going to talk about inducibility, but I'm going to stay on this document.

So number one, you agree that the brain is being studied 11 hours postmortem, right?

A. That's what they state here.

Q. Okay. And I'm going to bet you're going to agree with this too: CYP2E1 has a half-life of only about four hours in the absence of a stabilizing substrate or ligand as is the case after death, right?

A. I have no idea what you're getting -- where you're getting that from, so I -- I can't say.

MR. WATTS: Can we take a break?

MR. JANUSH: Sure.

THE VIDEOGRAPHER: We're going off the record. The time is 3:49.

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(Recess taken, 3:49 p.m. to 3:57 p.m. CDT)

THE VIDEOGRAPHER: We're going back on record. The time is 3:57.

BY MR. JANUSH:

Q. Passing you Plaintiffs' Exhibit 819.

(Whereupon, Deposition Exhibit P819, CYP2E1 and Oxidative Liver Injury by Alcohol, by Lu et al., was marked for identification.)

A. Thank you.

BY MR. JANUSH:

Q. So I left a little sticky on it to make it easier for you to turn to the page -- you'd stated before the break that you had no idea where I was getting that half-life from.

I'm presenting you with a National Institutes of Health manuscript addressing -- titled CYP2E1 and Oxidative Liver Injury by Alcohol, and the author is Yongke Lu and Arthur Cederbaum.

If you turn to page 9, where I put a sticker to make it easier for you --

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A. Uh-huh.

Q. -- you'll see a discussion concerning the half-life of CYP2E1. And so the author notes that -- towards the bottom of the first -- of the big paragraph: This system was used to evaluate turnover of the rabbit CYP2E1, which was rapid with a half-life of 3.9 h, hours, in the absence of a stabilizing substrate or ligand. Addition of the latter decreased the degradation of CYP2E1. We observed similar results in HepG2 cells expressing CYP2E1 as the half-life of human CYP2E1 was about 3 to 6 hours in the absence of a substrate or ligand, and was elevated in the presence of various substrates and ligands.

Do you see that?

A. Yeah, I see this --

Q. So that's where I was getting it from with respect to the published findings concerning the half-life of CYP2E1.

Had you ever, before today, studied about or learned about the CYP2E1 half-life in the absence of a stabilizing substrate or ligand?

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A. No, not specifically.

Q. It's kind of relevant when studying deceased brains, right?

A. I would note here this is -- it appears -- I haven't had an opportunity to read the whole paper, and actually, this appears to be a review.

It appears to me they're talking about a situation in cells. Cells have many ways -- healthy cells, right, live cells, they -- well, okay. So they mention that --

Q. Let me help you. I don't want to -- I'm not trying to --

MR. COHEN: Whoa. Whoa. Let him finish.

THE WITNESS: Excuse me.

MR. COHEN: Let him finish.

A. They say "this system." Above that, they appear to be talking about HepG2 cells. So yeah, right here: Huan and Koop established a tetracycline-controlled rabbit CYP2E1-expressing system in HeLa cells in culture. This system was used to evaluate turnover of the rabbit CYP2E1, which was

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rapid with a half-life of 3.9 hours.

This is done in live, viable functional cells. Proteins constantly turn over in live cells. This is part of just protein maintenance of -- normal protein levels, maintaining protein homeostasis. It's part of protein quality control.

Dead cells that aren't functional, I have no idea if they turn over proteins or at what rates or what half-life, any protein, certainly not CYP2E1. This -- therefore, in my opinion, this has no relevance to this Bhamre study.

BY MR. JANUSH:

Q. Wouldn't a dead brain have a lesser half-life than a living brain when it comes to CYP2E1 expression and -- and calculation?

A. No, not necessarily. Because again, functional cells maintain homeostasis, right? That means part of that is maintaining a certain level of proteins. You don't want to just make a ton of some protein and let it get out of control. You have to tightly control your functions. You're

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maintaining homeostasis on a live cell.
I don't think dead cells maintain homeostasis. I don't think dead cells do quality control. I have no idea what the protein turnover rate is for any protein in a dead cell, much less CYP2E1. This paper does not touch on that.
Q. But a dead cell would be more prone for CYP2E1's half-life to be shortened, not lengthened, right?
A. Once again, you absolutely cannot say that. Again, live functional viable cells maintain protein homeostasis. They maintain presently quality control. I would imagine dead cells don't do that.
Q. So when you say "I would imagine," are you just speculating?
MR. COHEN: Objection, form.
A. Speculating? No more than you are.
BY MR. JANUSH:
Q. Right. But I'm an attorney and you're the expert here, right?
MR. COHEN: Objection, form.
///

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BY MR. JANUSH:
Q. You're the scientist, I'm not, right?
A. You have not presented any data to me that shows that this half-life is relevant in a human body postmortem.
Q. I showed you a living human and what the half-life is --
A. Sorry. You didn't show a living human. You showed a living cell system.
Q. A living cell system. Fair enough.
A. That's an important distinction also, because this is cell culture. Cell cultures, especially HeLa cells, very famously, are aberrant. Normal cells don't grow on plastic like that, right? And HeLa cells are very famously not normal. There's a whole book written about this, a very popular scientific nonfiction book.
Q. And so you agree, though, that this was a study of a single human brain of a male subject, aged 50, obtained at autopsy following an instant death due to a traffic

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accident. You agree with that, right?
A. The authors state that it's a human brain from a male subject, aged 50 years, obtained at autopsy. Death was due to an instant -- was instant due to a traffic accident, excuse me, and the brain was obtained 11 hours postmortem.
Q. And the subject had no known neurological disorders, right?
A. That's a sentence in the Methods section.
Q. Yep. And nothing in this entire article is addressing acetaminophen, right?
A. Yeah. Again, I didn't cite it for any statement about acetaminophen. I cited it for a statement about CYP2E1 levels in the brain. So whether or not acetaminophen is in it is irrelevant.
Q. It's actually not irrelevant if CYP2E1 is something that induces -- excuse me.
If acetaminophen induces CYP2E1, that's not irrelevant, is it?
A. Well, again, there's no

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consistent reproducible, rigorous scientific evidence that acetaminophen induces CYP2E1. It's not a widely accepted idea in my field. In fact, there are conflicting data for it.
Q. The next article you address is Boutelet-Bochan from 1997. And with regard to Boutelet-Bochan, you take the position that the study did not measure CYP2E1 protein in the brain, right?
A. Correct, that's a statement that I've made.
Q. You agree that the study authors used standard reverse transcription-polymerase chain reaction and detected CYP2E1 mRNA in brain, right?
A. They used three different methods to look at messenger RNA.
Q. Yeah, I'm just addressing that one of the three.
And you agree that mRNA is the precursor to the protein CYP2E1, right?
A. The central dogma of biology is you have DNA that gets transcribed to RNA, which is then translated to protein.
Q. Did the authors actually detect

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CYP2E1 mRNA in nine of the ten brains that were studied?

A. Can you produce the article, please, just to refresh my memory.

Q. Sure can. Exhibit P820.

(Whereupon, Deposition Exhibit P820, Expression of CYP2E1 during Embryogenesis and Fetogenesis in Human Cephalic Tissues: Implications for the Fetal Alcohol Syndrome, by Boutelet-Bochan et al., was marked for identification.)

BY MR. JANUSH:

Q. And I'm going to turn your attention to page 445 at the Discussion, where at the bottom of the paragraph, above Figure 3, the authors write: With RT-PCR, the assay of highest sensitivity, strong signals were readily detectable in nine of ten human prenatal cephalic samples.

Do you see that?

A. I see that statement.

Q. Lack of detection in one sample remains unexplained, but may be due to genetic or environmental factors.

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And then it goes into the next page, and there's a Table 1. Do you see the Table 1 on the next page?

A. I do.

Q. And when we look at the RT-PCR, the brains there, the 10, we see nine of ten all with plus, plus, plus for brain tissue, intensity of observed signals.

Do you see that?

A. I see it. I also see below where they did northern blotting.

Q. I'm addressing RT-PCR, just say with me.

A. I also see below where they did northern blot --

Q. I know you want to testify about questions I haven't asked you, but I'm only addressing RT-PCR. Do you see that --

A. I would like to finish my answer.

Q. No, no, no. Your lawyer will get the chance to question you, and you can answer anything he asks you. But I'm only asking about RT-PCR.

So three pluses. And do you

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see at the bottom underneath the table, plus, plus, plus says strong?

Do you see that?

A. I see it.

Q. Okay. You left that out of your report in the sense that you left out that nine of ten brains demonstrated strong signals of mRNA CYP2E1, didn't you, under the RT-PCR analysis?

A. No, I address these data in my report by pointing out that there's a serious methodological flaw with the way they did the RT-PCR experiment.

Q. I appreciate that you addressed the flaw, and we're going to get there in a minute.

You left out that the authors found a strong signal of the precursor mRNA to CYP2E1 in prenatal human brains, in nine of ten prenatal human brains. You left that out of your report, right?

A. So as we discussed at length, the framework set up by the plaintiffs' experts is looking at what happens in the brain in relation to what we know about the

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liver, right.

You cannot do a -- you cannot -- you know, it's fine if you just want to use a -- by the way, extremely sensitive method -- to say, okay, there might be some CYP2E1 in the brain. I haven't disputed that in my report. I've said that there are negligible levels or little to no.

And when I say no, that's supported by data showing that in some studies when it's undetectable completely.

So everything has to be viewed here in reference to a comparison with the liver. The way that they did this RT-PCR part in Table 1 is severely methodologically flawed and can't be relied on for that comparison.

MR. JANUSH: Move to strike, nonresponsive.

BY MR. JANUSH:

Q. I only asked you if you left out of your report that nine of ten brains showed strong mRNA CYP2E1 expression.

A. Again --

Q. Did you leave that out of your

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report?
A. Again, the framework that we're working within, which was established in the plaintiffs' experts' reports, is that you have to consider the evidence -- consider data in the brain in the context of what we know about the liver. We discussed that at length. It's a very relevant piece of information here.
The relevant data is when you compare with the liver. And by the way, this is -- well, we can come back to that later.
So the relevant data here is that you compare to the liver, and that comparison is impossible with the RT-PCR method that they've used here. This is -- this is a method that's a binary result essentially -- it's essentially yes or no, is there some messenger RNA there. With that specific method, the answer was yes. With the other methods that they applied, the answer is either completely no across the board or conflicting --
Q. So --
A. -- equivocal.

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Q. So I don't see yes or no on the table. I see plus, plus, plus, plus for very strong signal, plus, plus, plus for strong, plus, plus for good, plus for detectable -- I guess that would be a yes or no -- and plus or minus for questionably detectable. And minus -- actually, that's the no. Minus for not detectable. And ND, not determined.
Do you see that underneath the table?
A. Oh, I see the definitions.
Q. Okay.
A. I --
Q. I just asked if you saw it. You answered me.
Now, on this, three pluses is the second-to-highest relative intensity of observed signals in nine of ten fetal brains for mRNA CYP2E1 expression, isn't it? Yes or no?
MR. COHEN: Object. Object to the form.
Go ahead.
BY MR. JANUSH:
Q. Yes or no?

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A. It's a meaningless result the way the experiment was done.
Q. Yes or no? I appreciate that you don't want to give me an answer, but it's a yes, right?
A. No, I'm giving you the scientific answer, the correct answer. You understand? The way that they have done this method, they cannot say, oh, there's a ton of people with CYP2E1 here.
They can say, oh, we've got a pretty strong signal in the PCR, but the PCR, again, the way that they've done it, they cannot compare with the liver, and that is our standard.
As we've discussed, as the expert -- plaintiffs' experts established in their framework for -- that I'm responding to.
Q. Dr. McGill --
A. The data are severely flawed.
Q. Dr. McGill, you criticize the manner in which the polymerase chain reaction was run because you say it should have been stopped during the exponential phase of

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amplification before the signal plateaus.
But in this case, the authors ran all polymerase chain reactions for 30 cycles, right?
A. Yes, which is what you should not do.
Q. And isn't it the case that by 30 cycles, when you run a polymerase chain reaction by 30 cycles, it's generally accepted that any identifiable signal will have reached a plateau?
A. That's exactly the issue. They -- the issue is not that -- the question is when they reach the plateau, right?
So when you do that, you can't make comparisons if you're stopping everything after they plateau. You've exceeded the dynamic range of the assay. You can no longer get a higher result for one sample that actually has a higher level. They would all have the same level.
So by stopping at 30 cycles, they have effectively ruined the experiment, unless their only goal is to say yes or no, there's messenger RNA for CYP2E1 there. So

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that's all you can get from that set of data.
Yes, they found some messenger RNA. How much was there? It's impossible to say.
Q. According to them, three plus, plus strength, right?
A. I don't believe anywhere in their methods section they described that grading system.
Q. Well --
A. So I can't assess what that means. This is meaningless data.
Q. Okay. So --
A. Other than, okay, they found some CYP2E1 messenger RNA.
Q. So -- but by comparison, given that you didn't provide your grading system on how you scored literature in this case, should we just discard your whole report as an irrelevancy?
MR. COHEN: Objection, form.
A. This is an entirely different question.
BY MR. JANUSH:
Q. Because it applies to you, it's

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different, right?
A. No, absolutely not.
MR. COHEN: No. Objection, form.
A. This is actual -- well, we'll just leave it at that. It's a different question.
BY MR. JANUSH:
Q. Dr. McGill, are you aware that Boutelet-Bochan is part of the same research group as Brzezinski, who published on CYP2E1 protein findings in 1999?
A. I may have seen the affiliations. I don't know these individuals. I don't know who they work with or what groups they're a part of.
Q. Okay. And I'd like to go to Brzezinski 1999 and --
A. Do you have --
Q. I will. I'm going pass it over. It's P821.
(Whereupon, Deposition Exhibit P821, Catalytic Activity and Quantitation of Cytochrome P-450 2E1 in Prenatal Human Brain, by Brzezinski

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et al., was marked for identification.)
BY MR. JANUSH:
Q. And in Brzezinski, up at the Abstract portion, on the right-hand side, the last six lines, the authors write: There was a dramatic increase in human brain CYP2E1 content around gestational day 50 and a fairly constant level was maintained throughout the early fetal period, until at least day 13 -- 113. The relatively low levels of the P450 isoform present in conceptual brain may be sufficient to generate reactive intermediates that elicit neuro embryotoxicity.
Do you see that?
A. I see their statement.
Q. Do you agree that Brzezinski et al., in 1999 established that unconjugated APAP can reach fetal tissues, including the brain, and is locally biotransformed into the toxic reactive NAPQI by CYP2E1 expressed in the fetal brain?
MR. COHEN: Objection, form.
A. You're -- sorry, you're asking

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me if this study established that?
BY MR. JANUSH:
Q. Yes.
A. Absolutely not.
Q. It's your opinion that there's no evidence of NAPQI in fetal brain sufficient to cause injury; is that right?
A. There's no evidence of NAPQI in the brain, period. We have no data about it in the fetal brain. So we assume, since, as you can see, for example, in the Allen Institute for Brain Sciences LMD microarray database, there's no substantial change -- there's no substantial difference in expression in the fetus and adults in the brain of CYP2E1.
So yeah, there's no reason to believe that fetal CYP2E1 is higher in the brain than in the adult. And we know you don't get adducts, at least in adult animals, in the brain, period. You don't get NAPQI.
Q. I'm going to move to a different section here. I'm going to address at section -- subsection (b), Studies of Other CYP450s in Brain.

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Here I'm going to address the Warner study, cited at footnote 104, addressed at paragraph 47. Published studies -- let's see.

Warner et al., 1988, purified total CYP450 content from rat brain and liver and found that the yield of P450 from the whole brain was 90 plus or minus 90 pmols over g -- over grams of tissue, which is approximately 1% of the level in liver microsomes.

Do you see that?

A. I do.

Q. I'll hand you both that, marked as 822.

(Whereupon, Deposition Exhibit P822, Regional Distribution of Cytochrome P450 in the Rat Brain: Spectral Quantitation and Contribution of P45Ob,e and P450c,d, by Warner et al., was marked for identification.)

BY MR. JANUSH:

Q. You also address that they, the authors, also measured CYP450 content in

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various brain regions and found that it never exceeded, you know, approximately 5% of the liver content.

A. Uh-huh.

Q. Do you see that as well?

A. I do.

Q. After making this statement, how can you go from the numbers addressed from Warner with the brain levels being approximately 1 to 5% of that of the liver to what you say in paragraph 48, where you address that CYP2E1 mRNA is approximately 1,000-fold lower in the brain than in the liver?

A. Yeah, easily.

Q. How do you get there?

A. Very easily.

So for starters, my statement about 1,000-fold lower in the brain than in the liver is about CYP2E1. This study is not about CYP2E1. Actually -- well, I'll come back to that in just a minute. There is some data relevant to CYP2E1.

What they've done in this paper is they've isolated total P450 content from

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the brain, and they show that it's, you know, in the range of 1 to 5% of what's in the liver. That's total P450 content, not CYP2E1. That's an important distinction.

It's also important to realize not all P450s are involved in drug metabolism. There are many other -- P450 is a superfamily of enzymes. It's quite large. There are many members, and they have many different functions, cholesterol synthesis, bioplastic synthesis, steroid synthesis.

So we don't know from the data in this paper which isoforms -- well, exactly what enzymes are contributing, what percentage of these P450s are actually relevant to drug metabolism.

In addition to that, there actually are some data -- the last paragraph of the Results section, that are -- I'm sorry, I'll slow down a little bit -- that are somewhat relevant to CYP2E1. So in that section, they state -- I'll go ahead and read it -- again, it's the last paragraph of the Results section.

Ethoxycoumarin O-deethylase

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activity -- which is a catalytic activity characteristic of both P450b and P450c -- was measurable in homogenates of thalamus and cerebellum. Catalytic activity, expressed as picomole of 7-hydroxycoumarin formed per hour per gram of tissue was 392 in the thalamus and 336 in the cerebellum.

I'll skip to the last sentence.

The corresponding value in homogenates of livers of control rats is 1,200 nanomole per gram of tissue per hour.

Ethoxycoumarin deethylation has been used in many studies as a marker of CYP2E1 activity. It can be catalyzed by other isoforms as well, but CYP2E1 contributes to that metabolism.

These 392 and 336 picogram -- picomole -- excuse me -- per hour per gram compared to the 1,200 nanomole per hour per gram, that means there's -- they detected about 0.03% of the activity in the liver in the brain.

So in other words, there's around or -- around 3,000-fold less in the brain than the liver. This is the only piece

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of data in this study that's relevant to CYP2E1, and -- as far as I'm aware, as far as I can recall, and that's -- actually makes my statement pretty conservative because I said 1,000-fold lower.

In addition, the 1,000-fold lower number, in the 16 studies that I cite specifically on CYP2E1, right, 12 of which I described in detail -- in contrast, by the way, to what Dr. Louie stated in his rebuttal report; he made the false claim that none of the studies I cited addressed CYP2E1 specifically.

Of the 16 studies, from those 16 studies, I've provided 12 numbers where they compared the brain levels to the liver, and if you average those 12 numbers, it's actually more than 1,000-fold lower in the brain than in the liver.

So again, my statement is actually conservative.

Q. And every one of the studies that you address fails to address acetaminophen, right?

A. I'm not citing those studies to

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make any statement specifically about acetaminophen. I'm citing those studies to make a statement about the relative expression of P4 -- CYP2E1 in the brain and the liver.

Q. Right, in the absence of any -- in the absence of any potentially inducible acetaminophen, correct? None of the studies you address have anything to do with acetaminophen?

A. Sorry. So again, with regard to the second part, I'm not citing them to --

Q. I know, I've heard it a hundred times. I get it. You're not citing them for the premise of saying that it has anything to do with acetaminophen.

A. I'd like to finish my response.

I'm citing them to support my statements in that section about the relative expression of CYP2E1 in the brain and the liver.

Q. And to be clear, you take the position that CYP2E1 is not inducible by acetaminophen, right?

MR. COHEN: Objection, form.

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A. There are no reproduce -- there are lots of conflicting data there. It's not widely accepted in my field because -- I'm sorry.

If your question -- if your question is does acetaminophen induce CYP2E1, that idea is not widely accepted in my field because there are no consistent rigorous, reproducible data showing that.

BY MR. JANUSH:

Q. Does ethanol induce CYP2E1?

A. I believe there's studies showing that ethanol induces CYP2E1.

Q. Do you believe it's biologically plausible for acetaminophen to induce CYP2E1?

A. I mean, again, I've seen no consistent reproducible data on that. I've not seen a clear mechanism by which it would happen, you know.

Q. Do you remember reviewing Dr. Pearson's report which had the single-cell Brain Bank image showing CYP2E1 expression in fetal brain?

A. Could you produce Dr. Pearson's

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report so I can refresh my memory?

Q. I probably can pull it up after a break and put it on the screen. I didn't anticipate, you know, using it to address your report.

You have -- you read it. You reviewed it. I'm asking if you remember the single-cell Brain Bank image that showed CYP2E1 activity?

A. My concern is that you may be using a name for it that I would not use, and so it's not -- I want to make sure it's clear that we're talking about the same figure.

Q. Be happy to pull it up after the break. Oh, perfect.

(Whereupon, Deposition Exhibit P856, Excerpt from Pearson Expert Report, was marked for identification.)

BY MR. JANUSH:

Q. It's actually hard to see. It's one -- one -- one page from Pearson's report. It was on page 18. I'm sure I can get it to the court technician electronically and pull it up and blow it up for you.

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I don't remember if you -- I don't know if you remember seeing that.
A. I recall seeing it.
Q. And? Do you have anything to comment on regarding it?
A. If you have a specific question, I'll be happy to comment.
Q. Are you disputing that CYP2E1 levels have been observed by the Brain Bank, I believe it is, in fetal brain?
A. Well, to be clear, this is messenger RNA data. It's not protein. So to say that CYP2E1 levels have been observed is not quite accurate based on these data alone.
So what this figure shows is a comparison, as I recall, a comparison of CYP2E1 messenger RNA levels in different regions of the brain.
I don't dispute -- so there's no comparison with the liver here. This is a critical point. When they say -- when he says that red indicates higher expression and green indicates lower expression, that's just relative to other parts of the brain.
Again, I've not disputed that

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there may be some P450 in the brain. What my report shows is that it's a negligible amount that's far, far lower than what's in the liver. And we know that in the liver, with very high CYP2E1 levels, you don't get clinically significant liver injury at therapeutic doses.
So if you have less than that in the brain, there's just no reason to think that therapeutic doses would have any effect there either.
Q. Do you agree that the brain's glutathione capacity is only one-fifth as compared to the liver?
A. Most reports that I have seen -- so this is a somewhat complicated question because the amount of glutathione in an organ at any one time can depend on multiple factors.
Generally speaking, what has been reported is that the levels are around 1 to 2, sometimes 3 millimole per liter in the brain. The liver, depending on what study you look at, it's reported anywhere between 5 and 10 millimole per liter in the brain.

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So I wouldn't necessarily say that it's one-fifth of what's in the liver. It depends on the study you're looking at, the conditions of the study and so on.
I would add, though, that it's still millimole per liter concentrations. As I said before, that's quite high. There's not a lot in the body that exists in millimole per liter concentrations. Certainly you don't get acetaminophen at millimole per liter concentrations after therapeutic doses, and since NAPQI -- only a small portion of the acetaminophen is converted to NAPQI, you definitely don't get millimole per liter concentrations of NAPQI.
So it's plenty of glutathione, what's been reported is -- should be plenty to detoxify NAPQI.
MR. JANUSH: Move to strike as nonresponsive.
Doctor, I had only asked you if you agreed the brain's glutathione capacity is only one-fifth as compared to the liver, so everything after that answer, I move to strike.

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Moving to my next question.
BY MR. JANUSH:
Q. Have you read Dr. Louie's rebuttal report?
A. I have.
Q. Incidentally, do you recall Dr. Louie citing to the Nuttall article, The impact of therapeutic doses of paracetamol on serum total antioxidant capacity?
A. I vaguely recall this, his reference to it in the study.
Q. In your report, you did not address the Nuttall publication, right, which studied the impact of therapeutic doses of acetaminophen taken over a period of time on serum total antioxidant capacity?
A. I don't recall if I considered it or not.
Q. Do you know why you didn't address it?
A. At the time, presumably, if I saw it, I deemed it irrelevant.
Q. In your entire report, did you address that the brain has a lower glutathione capacity than does the liver?

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A. Okay. When you say "glutathione capacity," we need to be real careful about what we mean there. I have described the glutathione concentrations in the brain from multiple studies, and I've also stated what a typical range of glutathione concentrations in the liver are.

Q. I'm talking about the protective capacity against toxins. Did you address that the brain has a lower glutathione capacity than does the liver?

A. As I've stated, in general -- I don't believe I've said it has a lower glutathione capacity. Glutathione concentrations in the brain are typically in the range of 1 to 3 millimole per liter; liver is typically in the range of 5 to 10 millimole per liter, based on most studies that I've seen.

Q. Moving on to paragraph 49, which is at page 42 of your report, you address...

I apologize, I've lost my spot. This is what happens when you're up for 30 hours straight. I'm going back to 40,

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forgive me, page 40. Studies of Glutathione in the Brain.

THE WITNESS: Do you mind if we took a break? I need to use the restroom.

MR. JANUSH: Yeah, no problem at all.

THE VIDEOGRAPHER: We're going off record. The time is 4:34.

(Recess taken, 4:34 p.m. to 4:43 p.m. CDT)

THE VIDEOGRAPHER: We are going back on the record. The time is 4:43.

BY MR. JANUSH:

Q. Going to page 40 of your report, starting with the case of -- the publication Griffith and Meister. Here we're addressing studies of glutathione in the brain that you address at paragraph 49, beginning on page 39.

Are you with me?

A. Yes.

Q. Griffith and Meister, you address that they found glutathione present in the normal adult mouse. Did this study

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have anything to do with acetaminophen?

A. Well, again, I wasn't citing it to support a statement about acetaminophen. I'm citing it to show that there's glutathione present in the brain at a pretty high concentration, but no, it didn't address acetaminophen.

Q. Cooper et al., 1980. This is a case where the adult rats were decapitated, and 30 minutes of total decapitation -- 30 minutes following total decapitation, decreased total glutathione.

Do you remember that?

A. My primary interest in that study was in the control rat levels, since that's what's relevant here. But if you want to produce the study, I'd be happy to look through it.

Q. I don't.

Did the study have anything to do with acetaminophen?

A. My response is the same as the one above. I'm not citing it to say anything about acetaminophen. I'm citing it because it shows that there's pretty high

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concentrations of glutathione present in the brain.

Q. Pileblad and Magnusson, 1988, rats were anesthetized with pentobarbital and polyethylene cannulae were implanted into each ventricle. And one to two days later, L-Buthionine-sulfoximine was administered intracerebroventricularly through cannulae. And the brain content of GSH was determined by high-performance liquid chromatography with electrochemical detection using N-acetyl cysteine as internal standard.

Now, do you remember that it was following a dose of L-Buthionine, a maximal depletion of GSH was seen in the cortex and brain stem? Do you remember that in this study?

A. Again, my interest in this study is the control levels, not the levels of treatment with buthionine sulfoximine. But just in case I slip into that language, just to be clear, I typically refer to that as BSO, so BSO.

That's -- that's not surprising that it would deplete glutathione in the

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brain because it's an inhibitor of the rate-limiting enzyme in glutathione synthesis. But again, my interest here is in the control levels.

Q. Where do you say that in your report? I didn't see that.

A. It says normal adult rat brain, so not BSO-depleted at all.

Q. Got it. Okay.

Jain et al., here newborn rats, 36 to 48 hours old, were treated with buthionine sulfoximine or saline control for three or nine days, and measured glutathione in the brain.

What was your interest in studying this -- this particular publication?

A. Again, same thing, I was interested in the control levels that they reported, so the saline-treated animals. I just mentioned that they were -- those were saline treated because -- you know, in case -- just full disclosure, I guess, of the way the animals were handled.

But saline treatment doesn't do anything. That's why it's a vehicle control.

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It's biologically inert.

Q. So I'm going to jump forward to the Kreis publication, which used magnetic resonance spectroscopy approach to measure glutathione concentrations in the brains of human infants delivered preterm or shortly after birth.

And you address, with respect to this, that they reported averages -- average values of 2.5 and 2.3 millimoles per kilogram for preterm and term babies, respectively, and that these values were higher than the reported concentration of 1.4 measured in human adult brains.

Did you notice that there was a standard of error on that Table 1A in Kreis of plus or minus .9?

A. I don't recall off the top of my head what the standard error was.

Q. So if, hypothetically, there's a standard of error of plus or minus .9, is there a meaningful difference between 2.5, 2.3, and by contrast, 1.4?

A. I would have to have way more data to make that assessment, way more

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information at hand.

Q. Well, I'm addressing numbers here, and so are you, and I'm addressing standard of error.

So if you are comparing 1.4 in terms of the measurement found in human adult brains as against the 2.5 and 2.3 measurement of glutathione concentrations in terms of millimoles per kilogram found in the babies' brains, mathematically speaking and from a scientific standpoint, if there's a standard -- a margin of error as high as .9, plus or minus, that may render the difference immaterial, right?

A. I cannot say based on the information that's in here. You would need a number of additional pieces of information such as what test -- what statistical test was done, how many animals they used in each group, what was the standard error -- preferably standard deviation on the other value that we're comparing with, not just that 0.9.

In addition to that, I'm not a professional biostatistician. I typically

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involve professional biostatisticians in my work.

Q. But you're using numbers and citing them to demonstrate differences between an adult brain, measured for glutathione concentration, and the brains of human infants delivered preterm or shortly after birth, also measured for glutathione concentration, and nowhere do you reference that there was a margin of error of plus or minus .9.

MR. COHEN: Object to the form.

BY MR. JANUSH:

Q. Right?

MR. COHEN: Object to the form. I think without showing him the study, this testimony is unfair.

But go ahead.

A. Yeah --

BY MR. JANUSH:

Q. Well, assume that I'm not lying --

MR. COHEN: I'm not accusing you of lying. I'm just talking about fairness.

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BY MR. JANUSH:
Q. -- and that I'm just trying to move on quickly and not show you a table just to have time wasted.
If, hypothetically, there's a standard of error, a margin of error of plus or minus .9 that was not addressed by you, that may -- that comprises a meaningful difference in -- and impacts the conclusion you reach regarding the differences between adults' and babies' glutathione measurements, right?
MR. COHEN: Objection, form.
MR. JANUSH: I can ask it more clean.
A. It was quite a long question. Would you mind --
BY MR. JANUSH:
Q. I'll break it down.
.9, plus or minus, margin of error should not have been ignored by you when assessing the Kreis publication if that margin of error existed between adults and babies, true?
MR. COHEN: Objection, form.

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A. Again, to make any statement about the statistical significance of that difference between 2.3, 2.5 and 1.4, I would need far more information.
Since I noted it here and specifically said it was higher, I assumed the authors did statistical testing and provided a result for that.
BY MR. JANUSH:
Q. Do you have 821 in front of you?
A. 821?
Q. Brzezinski, the Catalytic Activity and Quantitation of Cytochrome P-450 2E1 in Prenatal Brain?
A. I have it here, yes.
Q. And when we look at Figure 3, aren't we looking at a western blot of CYP2E1 protein in the prenatal human brain?
A. No. This is not a western blot. This is an RNA protection assay which quantifies messenger RNA.
Q. Oh, my apologies. That's the -- I can't even see right now. That's the ribonuclease protection assay.

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The immunoblot analysis is Figure 1.
Do you see that?
A. I do.
Q. And this is analysis of CYP2E1 content in microsome from prenatal human brain and adult rat tissues, right?
A. Yes, that's the title of the figure.
Q. So this is -- this is showing -- well, why don't you tell me.
What is meaningful about this to you?
A. So what's meaningful about this to me, what's particularly notable, is that it actually shows that the adult rat brain has a much lower CYP2E1 than the liver.
Q. What does it show you with respect to the human brain?
A. Well, again, it shows me that -- as I've said, I'm not disputing there might be some -- a little bit of CYP2E1 in the brain, including the fetal brain; it's just a negligible amount. So this is consistent with that. They've apparently

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detected a little bit of CYP2E1 in the brain, but again, it's lower than what they've detected -- much lower than what they've detected in the rat adult liver.
Q. And they've detected it in both the prenatal human brain at fetal -- let's see. I'm trying to compare it. It's hard through this reading.
I mean, what is clear is that there's a predominant band of immunoactive protein visible in each lane of the sample corresponding to CYP2E1, right?
A. I don't know what you mean by predominant.
Q. Well, that's what the authors noted, right?
A. I don't recall the exact wording that they used.
Q. Go to the bottom of Figure 1. The sentence states: A predominant band of immunoreactive protein is visible in each lane of sample and standard corresponding to CYP2E1.
A. Again, the data show that the levels are far lower than in the rat adult

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liver. They only loaded 10 nanograms, nanograms of protein for the rat liver. They've loaded microgram quantities, so on the order of a thousand-fold greater for the brain samples.

And despite adding a thousand-fold more protein, the levels still look a bit lower. When you take into consideration how much they loaded, it's far lower.

Q. Did the authors conclude that a minimal band exists or a predominant band of visible CYP2E1 protein, immunoreactive protein exists?

A. What they stated, if you look in the second paragraph up from that figure, the second-to-last sentence, it says their conclusion about that figure.

The enzyme was present at approximately 1.6 micrograms per milligram microsomal protein, similar to the amount in adult rat brain and about 150-fold less than the amount measured in the rat adult liver.

Q. Not 1,000-fold less as you've addressed in your expert report, right?

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A. Again, I've explained the way I came to that thousand-fold number. I cited 16 different studies, not just one. This was one of the studies that I included in that calculation.

Those 16 different studies provide 12 numbers comparing the levels in brain and liver, and if you average those 12 numbers, it actually comes out to more than a thousand-fold less than the brain compared to the liver.

So again, I was actually being conservative in my -- the number that I gave in my report.

Q. At paragraph 51 of your report, you address that at least two studies have demonstrated that chronic exposure to acetaminophen during early in utero development has no effect on brain glutathione levels later in life. And you address the Klein publication and Rigobello 2021, right?

A. Correct.

Q. With respect to Rigobello, do you agree that Rigobello 2021 concluded that

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acetaminophen-treated pregnant rats gave birth to offspring that were deemed to have neurological development -- developmental issues which the authors corresponded to increased oxidative stress in the brain?

A. I don't recall exactly what the authors concluded. I would need to see the study in front of me.

In addition, I can't comment on anything about neurobehavioral outcomes.

(Whereupon, Deposition Exhibit P825, Perinatal exposure to paracetamol: Dose and sex-dependent effects in behaviour and brain's oxidative stress markers in progeny, by Rigobello et al., was marked for identification.)

BY MR. JANUSH:

Q. You understand pregnant women aren't suing because their fetuses were exposed to Tylenol and that they had liver damage, right?

MR. COHEN: Objection, form.

A. My understanding of the plaintiffs' complaint is that they are --

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they claim that they -- their offspring suffered some neurodevelopmental adverse effects from in utero acetaminophen exposure.

So it's not about the liver. But again, we -- we used the liver as a framework, and that's due in large part to the fact that the plaintiffs' experts used the liver as a reference and framework.

BY MR. JANUSH:

Q. I'm just going to jump straight to the conclusion at page 5, paragraph 5, first three sentences only, and I'm going to move on.

In conclusion, our study describes behavioral and brain oxidative stress parameters altered in infant rats after gestational and lactational exposure to human-relevant doses of PAR.

PAR is paracetamol, right?

A. Yes. I disagree strongly with that conclusion, by the way, for the record. I'm more than happy to explain why.

MR. JANUSH: Sorry, this is Exhibit P825; and it's Rigobello, titled Perinatal exposure to

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paracetamol: Dose and sex-dependent effects in behaviour and brain's oxidative stress markers in progeny.

BY MR. JANUSH:

Q. But in this case, it's your hypothesis that there's adequate glutathione in the brain to accommodate any NAPQI production in the fetus, right?

MR. COHEN: Object to form.

A. I'm not sure what you mean by "in this case." Are you referring to this study in general?

BY MR. JANUSH:

Q. No, in general, in this litigation. I mean, you're here as an expert for the litigation, not as an expert on this particular piece of published literature, right?

A. I'm quite confident that there's sufficient -- if -- if any NAPQI could form in the brain after exposure to acetaminophen, I'm quite confident that there's enough glutathione to scavenge it. However, there's data showing that you don't get NAPQI in the brain, so it's kind of moot.

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Q. Do you agree that the findings of Brzezinski that CYP2E1 was found in the brain of rats are consistent with what Rigobello has found using subtoxic acetaminophen doses of 35 milligrams per kilogram or 350 milligrams per kilogram?

A. I have a number of comments about that. Their finding -- and I believe that was Brzezinski. Let me just double-check so I'm not misstating. Right. Okay.

Again, you remember in Brzezinski, they reported 150-fold lower levels of CYP2E1 in the brain. The lack of consistent reproducible effects on glutathione, for example, in this study is consistent with very low P450s in the brain, as Brzezinski reported.

Furthermore, this study can't be used really to say anything about NAPQI formation in the brain, and that's because, if I remember correctly, they're looking at 22 days, at least, after exposure. There would be no acetaminophen or NAPQI present, so any effect on glutathione would be due to

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something else.

Q. I'm going to jump to Studies of NAPQI Surrogates in the Brain and address the Fischer study that you cite. And that's on page 44 of your report.

A. Uh-huh.

Q. Dr. McGill, didn't Fischer use older liquid chromatography method that has a limit of detection in the 50 to 100 nanomolar range?

A. They used a method with radiolabeled acetaminophen, so they're counting radioactivity. I don't recall if there was any HPLC separation step or not before that.

This was an approach where you measure protein binding by -- you have a radiolabeled drug like acetaminophen. You inject the animals, harvest the tissue, and then basically -- basically wash the tissue to get rid of anything that's not tightly bound to it.

And then you measure the radioactivity that's -- I believe, if I remember correctly, that's how they did this

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study.

Radioactivity is pretty -- quite sensitive.

Q. If Fischer did use older liquid chromatography, as I've said, with a limit -- older chromatography would have a limit of detection in the 50 to 100 nanomolar range; wouldn't that be right?

A. I mean, liquid chromatography, first of all, characterizing it as older is odd. We do quite a lot of liquid chromatography today, and liquid chromatography, there are many different kinds of liquid chromatography.

Q. In 1981?

A. Oh, yeah, yeah, yeah. Liquid chromatography is one of the oldest methods to separate small molecules in samples. It's been around probably over a century would be my guess.

Q. What I'm getting at is: If -- if older liquid chromatography from 1981 had a limit detection in the 50 to 100 nanomolar range, that might not be able to detect levels of all APAP conjugates in the brain,

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right?
A. Levels of -- I -- are you asking about acetaminophen-protein conjugates?
Q. I am.
A. Just to make that more clear.
Off -- I mean, off the top of my head, I can't say. I also don't -- yeah. Again, radioactivity is -- it's a very, very sensitive approach. It's so sensitive it's prone to noise.
Q. Turning to the Bien study that you cite. Bien used a simpler colorimetric assay that has lower sensitivity than more modern methods do to study GSH; isn't that right?
A. No, that's not correct. One of the best methods available to measure glutathione is what's called the Tietze method. It's what I use in my laboratory.
Depending on how you set up the assay, it can be extremely sensitive. It's certainly -- I mean, I use it all the time in my studies with acetaminophen to look at glutathione depletion. It's certainly

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sensitive enough for that purpose.
Q. Is the Tietze method using -- using colorimetric assay?
A. Yes.
Q. And you disagree that it has lower sensitivity than more modern methods to study GSH?
A. Yeah. I also don't think sensitivity is an issue here, right, because you have -- sensitivity is important when you're trying to measure something that's very, very low abundance, right? But again, as I've stated, glutathione has presence in very high concentrations, millimole per liter. It's quite high for the body. Sensitivity is not an issue.
But whether it's an issue or not, these colorimetric methods can absolutely be extremely sensitive.
Q. Turning to Micheli (1993). Were rats dosed with 3,000 milligrams per kilogram?
A. That's my recollection of this study.
Q. And do you claim the authors

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reported only minor reductions of glutathione, 14-24%, in various regions of the brain?
A. Again, that's my recollection of the data.
Q. But didn't the authors in Micheli address, quote, from a physiologic standpoint, a 20 to 30% decrease of GSH levels is considered significant and able to start a reversible or irreversible toxic process?
Do you remember reading that?
A. I don't recall if they used those exact words. I'd be happy to see the report if you want to produce it.
Q. I don't.
A. In addition -- in addition, I disagree with that. We know again, if you look at my 2013 study, for example, in the liver, at 15 milligram per kilogram, we saw -- I don't remember the exact amount, probably 15, 20% loss of glutathione in the liver, there was no evidence of liver injury.
At the 75-milligram per kilogram dose, there was almost complete loss

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of glutathione in the liver. There was still no liver injury at that dose.
So no, that statement is categorically incorrect.
Q. So you disagree with the Micheli authors who wrote those words?
A. Yeah. In addition, they're only seeing this at the 3,000-milligram per kilogram dose, which again, has no relevance to maternal ingestion of therapeutic doses.
Q. But again, you yourself have recognized that rats have to be dosed significantly higher because they're poorer than mice in terms of animal study objects, study animals?
A. I've also explained that these doses -- that the rat model has no relevance to human therapeutic use or whether -- talking about large doses or not. These very large doses in rats result in these millimole per liter plasma concentrations of acetaminophen which you never see with therapeutic use of acetaminophen. Those are overdose concentrations. That's what you would see in an overdose patient.

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In fact, it's higher than what you see sometimes in acetaminophen overdose patients.

Q. At paragraph 56, where you address maternal use of therapeutic doses of acetaminophen and oxidative stress, this is the portion of your report where you address plaintiffs' claims relative to oxidative stress as a potential mechanism of action that leads to adverse fetal neurodevelopmental outcomes, right?

A. Yes. Well, I'm sorry, let me rephrase that.

This is the portion of my report where I address the issue of whether or not there's evidence that oxidative stress occurs in the brain with maternal use of therapeutic doses of acetaminophen.

Q. And you also address that no studies have been presented by plaintiff experts demonstrating that -- right, I mean, I'm going to quote it exactly.

A. Uh-huh.

Q. Demonstrating that therapeutic doses of acetaminophen caused oxidative

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stress in the human embryonic/fetal brain. Instead, plaintiff experts either fail to cite studies to support this hypothesis or rely on studies that use excessive doses or concentrations of acetaminophen.

Right?

A. Correct.

Q. Do you agree that it is ethically impossible to measure oxidative stress in the human embryonic/fetal brain and then follow up later to see if that test subject has neurological -- neurodevelopmental disorders?

MR. COHEN: Objection to form.

A. Well, again, I am not an ethicist. I can't comment on ethics. That's not what I'm here to discuss.

BY MR. JANUSH:

Q. But that testing would result in the death of the embryo and fetus, wouldn't it?

MR. COHEN: Objection to form.

A. I'm not a physician. I don't know what kind of sampling is possible without harming the child.

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BY MR. JANUSH:

Q. Do you agree that cell culture lines of evidence are relevant and should be considered in a true weight of evidence analysis?

MR. COHEN: Object to the form.

A. A formal weight of evidence analysis is not common in my field, so I can't comment on that.

In addition, the cell culture studies described by Posadas are irrelevant for human therapeutic use of acetaminophen. They have used, again, 0.5- to 2-millimole per liter concentrations for very long durations of exposure in those cell culture studies. That absolutely does not mimic human therapeutic exposure to acetaminophen.

BY MR. JANUSH:

Q. By the way, let me go back and ask you something that's sticking in my mind.

You addressed that the rat model has no relevance here, but you repeatedly included the rat model and rat model studies in your report, right?

A. I discuss --

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MR. COHEN: Object to the form.

Go ahead.

A. I discuss them in my report because, again, my report is, in part, a response to the plaintiffs' experts' reports who discussed some of these studies -- who discussed these studies.

BY MR. JANUSH:

Q. Do you have any methodology on oxidative stress?

A. Can you --

Q. In terms of how and why oxidative stress would not be created by virtue of prenatal exposure in utero to acetaminophen.

MR. COHEN: Objection, form.

A. Again, we're working within the framework of what happens in the liver as established by the plaintiffs' experts.

In the liver, you do not get oxidative stress after acetaminophen exposure without NAPQI formation. There's evidence -- we know that you don't get NAPQI formation in the brain after acetaminophen overdose -- overdose, much less therapeutic doses.

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BY MR. JANUSH:
Q. In reaching your conclusion, why did you not address the publication by Beck which found that even at the lowest dose of 125 milligrams per kilogram APAP given to rats, thiols appeared to be almost absent altogether in embryos studied, suggesting that GSH was depleted?
MR. COHEN: Objection, form.
A. First of all, if you're going to ask questions about the study, I'd like to see it.
And again, I would note, 125 milligram per kilogram -- milligrams per kilogram is not a human-relevant dose, not a therapeutic dose.
BY MR. JANUSH:
Q. It's a very small dose given to rats, isn't it?
A. Again, this gets into the issue of sub-hepatotoxic and therapeutic are not interchangeable terms by any means.
I also, off the top of my head, don't know what plasma concentrations that particular dose results in. It's likely much

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higher than human therapeutic concentrations.
Q. Why did you -- sorry.
Why did you fail to address the Baker et al., 2023 mouse study in which the scientists, including Dr. Pearson, gave pregnant mice 150 milligrams per kilogram and showed evidence for inflammatory and oxidative stress in the brain of the APAP-exposed neonatal mice using a dose that is therapeutic for mice?
MR. COHEN: Objection to the form.
A. Again, I'd need to see the study in front of me to assess it. I'm happy to discuss it if you can produce a copy of it.
BY MR. JANUSH:
Q. I'm not producing a copy, but it's on page 3 of your materials referred list or your reference list, so --
A. Yeah, I don't recall what their claimed evidence for oxidative stress is. I would need to review that if you want me to make a meaningful statement about it. Again --

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Q. We were hoping you would have reviewed it in your report, Dr. McGill.
MR. COHEN: Objection to the statement. That's not a question. That sounds like a lecture.
A. Again, the dose that you mentioned was far higher than therapeutic doses in humans.
BY MR. JANUSH:
Q. What do you believe an analgesic dose of acetaminophen is for a laboratory mouse?
A. I haven't reviewed the study on -- I haven't reviewed all the literature on analgesic doses of acetaminophen in mice. I can't really comment on that.
But the question is not necessarily about what's an analgesic dose in a rodent. The question is do the exposure levels in those models mimic exposure levels in humans. When you're giving such large doses, they absolutely don't.
Q. What do you believe is the appropriate dose of acetaminophen for a laboratory mouse?

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A. Appropriate dose to achieve -- sorry.
MR. COHEN: Objection, form. Go ahead.
A. Appropriate dose to achieve what?
BY MR. JANUSH:
Q. To test for inflammatory and oxidative stress in the brain of exposed neonatal mice.
A. Well, then I --
Q. You've criticized Dr. Baker and Dr. Pearson and their study group regarding 150 milligrams per kilogram. So if you were designing that study, what would you have done?
MR. COHEN: Objection, form.
A. If -- if I were designing a study to look at potential oxidative stress in the brain with acetaminophen, the dose that I would use is 14 to 15 milligrams per kilogram.
BY MR. JANUSH:
Q. AM404, paragraph 62, you address that: AM404 has been described as

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having a potential role in acetaminophen's mechanism of action for reducing pain and lowering body temperature. The proposed CNS pathways for the drug's analgesic effects include endocannabinoid, serotonergic, and nitric oxide pathways. The presence of AM404 in central nervous system and its potential effects was not described until recently. A limited number of studies have examined whether the biological effects of acetaminophen can be mediated by AM404, and only one study has examined the production of AM404 after acetaminophen use in humans.

Dr. McGill, isn't it true that AM404 literature is actually quite extensive and dates back to at least 2004, predating even the EPI?

MR. COHEN: Object to the form.

A. You asked a very broad question about AM404 literature. I don't know when the first mention of AM404 in the literature is. The data on acetaminophen and AM404, of which I'm aware, is what I would consider relatively recent, within the last -- I mean, it's hard to give a range for recent -- I

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don't know, 10, 15 years at most, that I can recall.

In addition to that, I wouldn't characterize it as a -- at least with respect to AM404 and acetaminophen as "a lot of research." I mean, compared to what? If you look at research on acetaminophen, it's been ongoing for, I mean, since it was synthesized and discovered in the late 1800s. There are tens of thousands of papers on acetaminophen, maybe more.

BY MR. JANUSH:

Q. AM404 in sufficient quantities has an analgesic effect; is that right?

A. I -- that's -- the analgesic effects and that sort of thing is not what I was asked to comment on.

Q. And AM404 has an analgesic effect because it operates on the central nervous system, doesn't it?

A. Again, a number of -- well, a number of pathways have been implicated in whatever -- whatever effects AM404 may have. Whether or not it actually acts on the central nervous system, I couldn't say for

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sure.

Q. At paragraph 66, you address that Högestätt et al., 2005, treated rats with 300 milligrams per kilogram of acetaminophen and were able to detect AM404 in the brain. However, a dose of 300 milligrams per kilogram of acetaminophen results in blood concentrations that vastly exceed concentrations in humans during therapeutic use.

Do you see that?

A. Uh-huh. Yes. Sorry.

Q. And then similarly, in paragraph 66, you also address Mallet, and again, deem that the authors administered rats with an overdose of 300 milligrams per kilogram and tested their tolerance to pain; is that right?

Let me ask a different question.

Do you deem -- do you -- despite what we've heard you say on video as you presented about rats and how immune they are to hepatotoxicity, you deem 300 milligrams per kilogram for rats to be an

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overdose administration?

A. Yeah. Yeah, for sure. Again, it results -- we know -- let's just take the Posadas study, which we've already discussed, a lower overdose than 300 -- 250 milligram per kilogram resulted in plasma concentrations of, again, 1 millimole per liter; that is 1,000 micromole per liter.

Maximum therapeutic plasma concentrations in a human are 100 -- around 130 micromole per liter, so it's at least 7.6-fold higher plasma concentrations. That has absolutely no relevance to maternal ingestion of therapeutic doses of acetaminophen.

Q. When you know an animal such as a rat is ten times less susceptible to liver injury than mice, should scientists scale their studies to better test for the potentially injurious outcome they are studying when using rats as test animals?

A. We've been over the animal equivalent dosing. I've shared my opinion on that.

We know a lot about

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acetaminophen. We know the therapeutic plasma concentration. I have no reason to believe that we shouldn't aim for those concentrations in a rat, for the studies -- types of studies that we're discussing related to the brain.

Q. Aiming for concentrations of human therapeutic doses in rats leads -- necessarily leads to ignoring that the rat is ten times less susceptible to liver injury than mice, doesn't it?

A. No. So again, I have no reason to believe that the brain is more susceptible to -- or excuse me, that the rat brain is less susceptible to acetaminophen. In fact, in general -- I'm sorry, let me start again. I want to make sure I'm saying it correctly.

I have no reason to believe that the rat brain is more resistant to acetaminophen as a matter of -- well, I'm sorry. I'm -- I need to rephrase.

Essentially, I have no particular reason to believe that we need to adjust the dose to look at that in the brain. Yeah, I mean, the brain in general is

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obviously resistant to NAPQI formation, right, because we don't see any NAPQI formation in the brain, even with massive overdoses of acetaminophen. And there's very little -- little to no CYP2E1 in the brain.

Q. Talking about humans, you do not know the dose of acetaminophen necessary to affect fetal neurodevelopment, right?

A. Again, I'm not here to address studies on neurodevelopmental outcomes or things -- I'm not here to address neurodevelopmental outcomes.

Q. And you don't know the duration of use at therapeutic doses that would affect fetal neurodevelopment, right?

A. Again, I'm not here to address neurodevelopmental outcomes. We know the concentrations and duration of exposure in human -- to acetaminophen in humans at therapeutic doses, and we know that the rat model and that these high doses, whether you're in mice or rats, do not mimic that human exposure.

Q. In this case, are you assuming that there's a perfect solution for the fetus

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that neutralizes the CYP2E1?

A. Neutralizes the CYP2E1?

MR. COHEN: Object to the form.

BY MR. JANUSH:

Q. Excuse me, that neutralizes the -- yeah, the CYP2E1. That's exactly what I meant.

In other words, you address that there's sufficient glutathione to handle any expression of CYP2E1. Are you assuming that that's a -- there's a perfect solution that -- for the fetus that neutralizes CYP2E1?

MR. COHEN: Object to the form.

Answer, if you can.

A. Right. Again, I'm not saying anything about neutralizing CYP2E1. Glutathione neutralizes or detoxifies NAPQI.

BY MR. JANUSH:

Q. I meant to say that. I apologize. I've been up for 30 hours straight. I meant to say NAPQI.

MR. COHEN: Do you want to reask the question?

THE WITNESS: Yeah, please, if

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you don't mind, I'm sorry.

MR. JANUSH: Yeah.

BY MR. JANUSH:

Q. Do you believe that there's a perfect solution for the fetus that neutralizes NAPQI expression?

A. What we know is that you have, number one, very little P450 in the brain relative to liver. My studies described in my report demonstrate that.

What we know is that you have glutathione at millimole per liter concentrations in the brain. Again, studies described in my report show that.

We also know that in order to have toxicity -- significant clinical liver injury in the liver with acetaminophen, which has far more CYP2E1, you would need an overdose. Therapeutic doses don't cause any injury in the liver, despite having much more CYP2E1 than the brain.

So you certainly wouldn't expect that an organ like the brain with much, much less CYP2E1 would be susceptible to injury at therapeutic doses.

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I guess I'll stop there.
Q. In your report, you mention that your independent research group has been primarily funded by UAMS and by the American Association for the Study of Liver Diseases Foundation, with additional funding from GlaxoSmithKline and Haleon, Bergstrom Nutrition and the Federal Transit Authority.
What kinds of research have you performed that was funded by GSK?
A. I'm under a contractual obligation not to share the details of those studies, so I can't comment on that, except to say that it's not related to effects on the brain of acetaminophen.
Q. Is it related to acetaminophen or paracetamol at all?
MR. COHEN: If you can answer that without violating any agreements, go ahead. But if you think you might be violating an agreement, then he can't answer that.
A. I am not a hundred percent sure if I can answer that question, so I would prefer not to comment on it.

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MR. JANUSH: We're going to mark this spot of the transcript for further follow-up.
BY MR. JANUSH:
Q. You've received $107,000 from Haleon in connection with something called Project HEP, part 2. What's that?
A. This is a -- what I can say about it is that it's an extension, right? Haleon was a company that split off of GlaxoSmithKline, and that project is an extension of the prior project with GlaxoSmithKline. I'm under the same contractual obligations not to discuss any details.
Q. Does your contract ban you from even confirming whether or not you are studying acetaminophen?
A. As I said, I'm not a hundred percent sure. I don't recall the exact language of the contract. I don't feel comfortable saying one way or the other.
I can say that it's not related to the brain. I think I'm safe saying that.
Q. Haleon distributes

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acetaminophen products, right? Like Advil Dual Action with acetaminophen and Panadol?
A. So my understanding is that GlaxoSmithKline was a manufacturer of acetaminophen in countries outside the US. I don't recall -- I don't know exactly which countries.
Since Haleon split off of that, I don't know what -- exactly what Haleon's relationship is to the manufacture of and sales of acetaminophen.
MR. JANUSH: Can we take a break?
MR. COHEN: Sure.
MR. JANUSH: Go off the record.
THE VIDEOGRAPHER: We are going off record. The time is 5:30.
(Recess taken, 5:30 p.m. to 5:43 p.m. CDT)
THE VIDEOGRAPHER: We're going back on record. The time is 5:43.
(Whereupon, Deposition Exhibit P832, McGill Invoices, was marked for identification.)
(Whereupon, Deposition

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Exhibit P832B, McGill Invoice, was marked for identification.)
BY MR. JANUSH:
Q. Dr. McGill, I've premarked and given you Exhibit P832 and P832B. These are the invoices that we have from you to David Cohen, counsel that's sitting across the table from me, and Amy Ragone of Butler Snow. They reflect billings from January 16, 2023 through September 4, 2023.
Have you had an opportunity to review these billings?
A. Yes.
Q. Are these an accurate representation of your invoicing from your inception of expert work through the present date?
A. They appear to be the invoices -- copies of the invoices that I submitted.
MR. JANUSH: Thank you, Dr. McGill, for your time today. I have no further questions.
THE WITNESS: Thank you very much. I -- thanks, everybody.

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MR. COHEN: Do we need change or can I just ask two questions?

(Technical comments off the stenographic record.)

EXAMINATION

BY MR. COHEN:

Q. Just real quickly, Dr. McGill.

Earlier in the day, counsel asked you about Exhibits 804, 805 and 806, which are studies that are referenced in your expert report on which you and Dr. Jaeschke are coauthors, among others; is that correct?

A. I remember discussing the articles.

Q. Okay. And it may have been inadvertent, but counsel said, I think, that these studies, which are cited in your expert report, address the neurotoxic results of acetaminophen.

Do you remember that?

A. If he made the statement, then -- these are not studies of neurotoxicity, so that would be inaccurate.

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Q. And that was my question: If he made that statement, was that an error?

MR. JANUSH: It was.

A. I feel like it must have been.

BY MR. COHEN:

Q. These studies do not address neurotoxicity, do they?

A. No.

Q. Okay. And he also pointed out that these studies indicate that McNeil, in part, funded some of Dr. Jaeschke's work?

A. I believe that's what he was -- yeah, suggesting.

Q. Do you remember that?

A. Uh-huh.

Q. Do the studies also indicate that the NIH and other funding sources also funded Dr. Jaeschke's laboratory?

A. I believe some of them indicated that. I mean, he certainly received funding from multiple other sources.

Q. You were asked earlier by counsel about Exhibit 813, P813, which is the Nitsche study from 2017.

Do you remember that?

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A. I do.

Q. And do you remember counsel asked you about the conclusion and the concluding sentence in the conclusion that's cited in your expert report beginning with the word "However, our findings suggest that maternal use of acetaminophen at the currently recommended dose is unlikely to lead to accumulation of potentially toxic levels in the fetus."

Do you remember that?

A. Yes.

Q. Can you point to -- or tell us where the data are in the study that support that statement?

A. Well, this statement is about levels in the fetus, and they specifically reference potentially toxic levels, and so if we -- if we're talking about levels of acetaminophen, the data are shown in Figure 1 so --

Q. What does Figure 1 indicate, briefly?

A. It's -- well, yeah. It's -- I think -- I believe it's consistent with their

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statement there, and it indicates that there's no accumulation or greater concentration of acetaminophen in the fetus than in the mother. So it's not reaching toxic levels.

MR. COHEN: Okay. That's all I've got. Thank you, Doctor.

THE WITNESS: Thank you.

MR. JANUSH: No further.

THE VIDEOGRAPHER: Okay. This concludes today's deposition. We are going off the record. The time is 5:48.

(Time noted: 5:48 p.m. CDT)

--o0o--

CERTIFICATE

I, MICHAEL E. MILLER, Fellow of the Academy of Professional Reporters, Registered Diplomate Reporter, Certified Realtime Reporter, Certified Court Reporter and Notary Public, do hereby certify that prior to the commencement of the examination, MITCHELL R. McGILL PhD was duly sworn by me to testify to the truth, the whole truth and nothing but the truth.

I DO FURTHER CERTIFY that the foregoing is a verbatim transcript of the testimony as taken stenographically by and before me at the time, place and on the date hereinbefore set forth, to the best of my ability.

I DO FURTHER CERTIFY that pursuant to FRCP Rule 30, signature of the witness was not requested by the witness or other party before the conclusion of the deposition.

I DO FURTHER CERTIFY that I am neither a relative nor employee nor attorney nor counsel of any of the parties to this action, and that I am neither a relative nor employee of such attorney or counsel, and that I am not financially interested in the action.

MICHAEL E. MILLER, FAPR, RDR, CRR
Fellow of the Academy of Professional Reporters
NCRA Registered Diplomate Reporter
NCRA Certified Realtime Reporter
Certified Court Reporter
Notary Public

Dated: September 11, 2023

INSTRUCTIONS TO WITNESS

DATE: September 11, 2023

Please read your deposition over carefully and make any necessary corrections. You should state the reason in the appropriate space on the errata sheet for any corrections that are made.

After doing so, please sign the errata sheet and date it.

You are signing same subject to the changes you have noted on the errata sheet, which will be attached to your deposition.

It is imperative that you return the original errata sheet to the deposing attorney within thirty (30) days of receipt of the deposition transcript by you. If you fail to do so, the deposition transcript may be deemed to be accurate and may be used in court.

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ACKNOWLEDGMENT OF DEPONENT

I, MITCHELL R. McGILL PhD, do hereby certify that I have read the foregoing pages and that the same is a correct transcription of the answers given by me to the questions therein propounded, except for the corrections or changes in form or substance, if any, noted in the attached Errata Sheet.

_____
MITCHELL R. McGILL PhD DATE

Subscribed and sworn to before me this

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My commission expires: _____

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Notary Public

LAWYER'S NOTES

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WORD INDEX